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BRITISH MEDICAL JOURNAL

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PSYCHIATRY AND GENERAL MEDICINE*

BY

Sir DAVID HENDERSON, M.D., F.R.C.P.

Professor of Psychiatry, Edinburgh University; Physician Superintendent of the Royal Edinburgh Hospital for Nervous and Mental Disorders

I regard it as a great honour to have been invited to deliver a lecture in the Birmingham Medical School, where so much is being done to effect a liaison between psychiatry and general medicine. This closer integration is greatly to be desired because of the further contribution which may be made to the science and art of medicine. We have worked far too long in considerable isolation, and in consequence we have been too localized, too one-sided, too much in the nature of special pleaders, when a more comprehensive outlook would have led to greater benefit both to our patients and to ourselves. The gap which exists between psychiatry and general medicine (which is inclusive of surgery, obstetrics, gynaecology, etc.) is still far too wide; it requires to be rebridged, and it is my purpose here to consider how that may be effected. The task is a formidable one, because prejudices and faults which are difficult to overcome have been developed on both sides. However, I shall try to examine the position as dispassionately and fairly as possible.

Aim of the Medical Profession

Our profession is vitally concerned not only with the treatment of persons who are ill and in need of help but also with the even greater responsibility of understanding the fundamental facts of human nature and of biology, which concerns itself equally with the health of the individual and the welfare of society. That wider concept of our aim is in process of being more generally recognized, so that it is customary in some universities to inform medical students at the very beginning of their career that medicine is not purely an objective mechanistic science but rather a sphere of work which embraces all the interactions of mind and body. Such a changed outlook constitutes a distinct advance, and prepares the mind of the student to think much more comprehensively of what is ahead of him. It indicates that we have departed a long way from the conception of illness as an organic disease, and it suggests that the multiple causative factors which may exist should be investigated at both a psychological and a physiological level. The result should lead to greater clinical acumen, more accuracy in prognosis and diagnosis, and more successful treatment. The fact that attention is being centred on the whole man will inspire greater confidence both in patient and in doctor, and healing will become more easily managed owing to the neutralization of fear, anxiety, and apprehension, which are so often at the root of all illness.

All who successfully practise the healing art recognize the above principle. The particular agent employed might have been a priest of experience at one or other of the Aesculapian temples; Mesmer or one of his disciples; a royal or other distinguished person who used the prerogative of "touch"; the Christian Science Church; or Lourdes; or Gheel; or any other person or place which inspired confidence. That that is not an antiquated theory is amply confirmed by a book recently published, *Stress and Disease*, by H. G. Wolff, whose work on psychosomatic disorders is so well known. A review of that book (*Lancet*, 1953, 2, 763) points out that "man's reaction to man may be at least as important as his reaction to a microbe." It is therefore not so surprising as it might seem that Wolff, as a result of his interesting and intensive study of 739 subjects, concluded that the main therapeutic aim to effect recovery was to produce tranquillity and freedom from sustained hostility and resentment. It was only then that satisfactory cures could be attained—surely a powerful argument in favour of the psychosomatic approach.

Attitude Towards Mental Illness

In earlier times, to which reference has already been made, it is probable that the main differentiation of illness was effected in terms of death, recovery, or apparent incurability. And it is a fair guess to suggest that the vast majority of psychotic and nervous patients belonged to the incurable class. No doubt it was their recalcitrancy, their inability to respond—either to kindness or to a beating—which led eventually to their exclusion from society. They were not understood; they were stigmatized as wicked and perverse rather than as suffering from an illness which, under proper conditions, might respond to treatment. I regret to say that I believe we may have helped to manufacture many of them by the harsh and arbitrary methods of treatment which were in vogue; padded rooms, excessive sedation, the too hasty employment of powerful physical remedies. In passing it is of some interest to comment on the fact that such conditions as multiple personalities and florid conversion hysterical states, often the results of ill-advised examinations, rarely occur to-day.

It seems to me that it is justifiable to state that our practice in relation to mental illness then was very similar to our attitude towards the delinquent classes to-day. Constructive rehabilitation measures—legal, medical, and social—for those who for one reason or another fail to make a satisfactory social adjustment because of mental illness or delinquency, are still sadly lacking.

*A lecture given in the Faculty of Medicine of the University of Birmingham on January 8, 1954.

Great advances have undoubtedly taken place; our therapeutic equipment is much more efficient and varied, but in the face of failure we are much too slow and unwilling to admit our incompetence and lack of knowledge. We behave much as our forebears did; we overrationalize, we project our disappointments on the lack of co-operation of our patient, or question the genuineness of his complaints, or call him a wicked, immature person with a decided negative transference. This, of course, is the identical attitude adopted by those who criticize art, or poetry, or music, or anything else they neither understand nor like.

A Dangerous Trend

In the development of our special medical skills we have watched the progress of general medicine by way of biochemistry, biophysics, physiology, and therapeutics, while psychiatry has gained its particular stimulus through the study of biology, personality structure, psychogenesis, and psychotherapy. Such a parallel but divided course has constituted a dual misfortune, because general medicine became too organically minded, too mechanistic, almost too pathological, while psychiatry lost its objectivity and became dominated by the subjective, emotional, and hypothetical. The somewhat absurd stage has now been reached where, so far as the latter is concerned, a basic medical training is no longer regarded as a necessary prerequisite for the work of the clinical psychiatrist. Truly that is a most serious and disastrous state of affairs. It cuts across all medical tradition and practice. We must not be content with the thought that lay therapists are not accorded official recognition; that is not enough, because, irrespective of the lack of official recognition, certain institutes and clinics have drawn up comprehensive programmes of instruction (of which personal analysis is usually an integral part) to which many lay persons are attracted.

I regard such a development as dangerous and reprehensible; it tends to undermine the whole structure of medical education; it requires the critical attention of every faculty of medicine and of the General Medical Council. How has all this come about? Largely, I believe, because orthodox medicine has so often failed to give due consideration to the psychological factor which is so much part and parcel of all illness. There is truth, indeed, in the statement that the *malades imaginaires* are the reward of the quack and the despair of the honest physician. In consequence the advocates of the policy of training lay psychotherapists justify themselves by pointing to the large number of nervous invalids in need of help, and the scarcity of trained personnel to deal with them. For my part, I do not accept that statement as a valid argument. The management of the greater number of psychoneurotic states is not an essentially specialist problem, but one which should be brought within the scope of a well-trained general practitioner.

Some, at least, of the mistakes and difficulties I have mentioned would be avoided if we were more historically minded, and had more ability to correlate our clinical observations. It is so disappointing to find that so many of our colleagues seem to believe that psychiatry began to function only from the Freudian era, while others, even more modern, base their practice on the wonders of present-day physical therapy. This is evidenced by those candidates for senior appointments who, in support of their claims, proudly state that they have had a personal analysis, have introduced electric convulsion therapy into their out-patient departments or consulting-rooms, regard insulin coma as a specific for "early" schizophrenia, or have performed a transorbital leucotomy. It would be infinitely more encouraging if they expressed an interest in the broader aspects of psychiatry, in its history and its literature. It is more through good clinical observation and individual work with patients that we are likely to be successful in our search for so much which is still unknown. I do not want to flog that issue too much, but, in order to keep a reasonable perspective before us, allow me to give you a glimpse of the thought and work of 100 years ago.

A View Held 100 Years Ago

In 1854 Forbes Winslow's first Lettsomian Lecture was entitled "The Psychological Vocation of the Physician," and what he said then is so apropos of my thought to-day that I venture to give a brief quotation. He wrote:

> "I have undertaken in my first lecture to illustrate the special psychological attributes of the physician—to claim for the cultivators of medical science higher and more exalted functions than those usually assigned to them—to consider the physician in his spiritual character, as having at his command, and under his control, a *medicina mentis* as well as a *medicina corporis*—agents of great power and magnitude which have not been sufficiently recognized or appreciated. It will be my object to establish the close connexion between the Science of Mind and the Science and Practice of Medicine, and to illustrate the true philosophic character of the professors of the healing art.
>
> "The physician is daily called upon, in the exercise of his profession, to witness the painful effect of mental emotion upon the material fabric. He recognizes the fact although he may be unable to explain its rationale. He perceives that moral causes induce disease, destroy life, retard recovery, and often interfere with the successful operation of the most potent remedial means exhibited for the alleviation and cure of bodily disease and suffering. Although such influences are admitted to play a part, either for good or evil, I do not conceive that, as physicians, we have sufficient appreciation of their great importance. . . . Many a disease is the *contre-coup*, so to speak, of a strong moral emotion; the mischief may not be apparent at the time, but its germ will be nevertheless inevitably laid."

That short extract indicates that many of the great physicians and psychiatrists of the past had an admirable knowledge of psychosomatic disorders, and it is surprising that the significance of the principles which they laid down is only now being fully recognized. Forbes Winslow and others like him, and some far greater than he, were broad-minded philosophical clinicians imbued with a wide outlook who, although they worked under great difficulties and against much prejudice, helped and cured their patients because of their interest and understanding of them, and because of the love of the work they were doing. To-day we are in a much stronger position than our forebears. Our technical resources have been greatly increased. We can readily enlist the help of chemists and physicists, psychologists, physiologists, brain surgeons, neurologists, all of whom can contribute their particular quota. But in our search for the new let us hold on to the experience, the wisdom, and the humanitarianism of the past.

Important Landmarks

We may now consider in more detail the biological concept which I have mentioned, and refer briefly to some of the more important landmarks which have contributed so much to an intensification of psychiatric thought and practice.

The descriptive and, may I add, the philosophical period of Kraepelin, Maudsley, Clouston, and their contemporaries was an era of brilliant achievement which has proved to be the foundation of many of the great advances which have occurred since. That is a categorical statement, no doubt, but yet I believe it will be substantiated by any fair-minded person who cares to examine the position for himself. It was the foundations and classifications of those men which inspired Adolf Meyer, in the first decade of this century, to describe his conception of psycho-biological principles, with particular emphasis on reaction types, and the study of the individual in his social setting. It is no exaggeration to say that his views and his teaching transformed the standard of psychiatric work not only in the United States but throughout most of the civilized world. His impact here in Britain was enormous. He was one of the great psychiatrists (clinical and neuro-pathological) whose penetrating, investigative mind made it imperative for him, in sizing up every case, to be in possession of all the facts derived from

whatsoever source, personal or environmental—a lesson and a discipline which it is essential for us to remember to-day.

During the same period Freud started from a much more specialized angle than Meyer, but it was not long before the ingenious technique of psycho-analysis for the treatment of certain psychoneurotic states broadened out into a system of philosophy and psychology which has received universal recognition. Whether Freud has done more for the advancement of an understanding of human nature than any other man since Aristotle might raise considerable argument, but he certainly infused an interest and a stimulus into psychiatry and philosophy which still persists. Our dreams, our words, our acts mean something, and even the weird and bizarre symptomatology of nervous and mental disorders which baffled our understanding for so long can be interpreted and understood. Freud brought us nearer the core of things.

Again, from a totally different and even wider angle, Clifford Beers, the young Yale undergraduate, promulgated the doctrine of mental hygiene as an educative force towards better, and healthier, and more understanding living. The small Connecticut Society for Mental Hygiene, which he founded in 1908, has grown into a mighty World Federation movement.

Each approach which I have mentioned has taken us a stage or two further. The work done has been complementary, and has been directed to the particular purpose of coming to a fuller understanding of nervous and mental illness so that it may be prevented and remedied.

Problem of the Nervous Invalid

We need help from all quarters in dealing with the tremendous problem presented by the nervous invalid—a problem which, whether in peace or whether in war, creates serious and numerous casualties, and one which, without wishing to be sensational, may be said to be eating into the life-blood and efficiency of every nation. At no time has it been more necessary to direct attention to the imperative need for a better appraisal of the interactions of mind on body, and body on mind—a study which can be successfully accomplished only by the friendly co-operation of psychiatry and general medicine.

A study of the epidemiology of psychoneurotic and psychosomatic disorders leaves us in no doubt of the upward trend which is occurring. Our out-patient departments are inundated with new cases, our in-patient accommodation is inadequate, and, furthermore, we have neither the quality nor the quantity of skilled medical personnel to deal adequately with those often so desperately in need of help. It may be that this present position merely reflects the disturbed social and economic conditions under which we are living, but it is more probable that the real cause lies a good deal deeper and is centred, to a certain extent, in the increase of the selfish, individualistic, irresponsible types in whom a sense of loyalty to family, friends, or organization is so greatly lacking. Wherever the fault lies it needs tackling, and one of the ways in which this may be done is to see to it that the doctors of the future are trained to investigate the psychological and social factors which may operate in any form of illness. It is partly a problem of medical education which will be referred to later.

But before I pass to another topic may I be allowed to comment on a group of psychosomatic disturbances which have always been of great interest to me. I refer to cases of pregnancy and child-bearing in which the interplay between the psychological and the physiological components must be very intense. In most cases, fortunately, the personality remains intact. Clouston was probably quite correct when he stated that nature seems to have a remarkable ability to look after the pregnant woman. But that is not always the case; many failures occur, and many difficult situations arise which lead to disturbances of thought and conduct that may be disastrous and tragic. Helene Deutsch has explained all this very well in her book *Psychology of Women,* in which she points out "that there is hardly a woman in whom the normal psychic conflicts do not result in a pathological distortion, at some point, of the biologic process of Motherhood." I think, for instance, of those cases in which there is (1) a fear of transmitting nervous or mental disease; (2) an unwanted child; (3) marital disharmony; (4) infertility; or (5) repeated abortion. When such conflicts are present there may be a rich display of symptoms which operate like a conditioned reflex—for example, nausea, vomiting, miscarriage. This is indeed a field in which the closest possible co-operation should prevail between the obstetrical and psychiatric departments.

It is not a very far cry from the mother to the nervous child—to an understanding of its psychological as well as its physical needs. Kanner has always insisted that the problems presented by such children lie in the patients themselves rather than in their organs—for example, poor school progress, enuresis, food capriciousness, temper-tantrums, nail-biting, fear reactions, epileptic phenomena; others may exhibit tics, headache, sleep disturbance, sex problems, stealing. A fascinating and rewarding field for study if we believe, as we should do, that the sense of security and confidence attained in childhood passes on into adult life. It is both disappointing and surprising that, under these circumstances, there is still so little co-operative effort between psychiatrists and paediatricians.

Personality Disturbances

The above discussion has demonstrated many conditions involving body and mind which are not susceptible of care until we have understood and treated the psychological traumata which have created them. In contrast attention can now be directed to those personality disturbances involving emotional, ideational, or intellectual impairment which are due to or dependent on objective organic lesions. It is fairly certain that, here, no real betterment will occur until the organic cause has been successfully dealt with. We can think, for instance, of the anoxaemias which can produce quite devastating effects, as evidenced by the sensitive, suspicious, irritable, aggressive, and even murderous reactions of explorers, mountaineers, and others who may find themselves in dangerous straits due to exposure, hunger, or other circumstances leading to deoxygenation. In toxic exhaustive conditions such as alcoholism, malarial infection, and so on, intense fear reactions are in the ascendant, and often are accompanied by delirium with its dangerous sequelae. And then there are the great variety of inflammatory and/or destructive lesions of the brain structure due to primary tissue change or dependent on vascular disturbance. Nor should one forget to mention the personality changes which not infrequently may be the aftermath of leucotomy operations.

Some day, perhaps, we will gain a little more knowledge of the epileptic mechanisms, what determines their particular form, whether there is a particular epileptic temperament or character, to what extent the psychic epilepsies, the post-epileptic and fugue states, are linked up with emotional factors—for example, the aggressive behaviour of the psychopath. The pre-senile groups are still inadequately understood, and often not recognized, and we know practically nothing of how they arise or can be prevented. Brain tumours masquerade far too frequently as dyspepsias or neurasthenic states, when a careful neurological examination whould often allow a correct diagnosis to be made at a remedial level. Great and quite unnecessary difficulty seems to circle round the correlation of the mental and physical symptoms in cerebral vascular disease, especially in relation to the vessels supplying the basal nuclei. The labile emotional state, the personality change, the lack of concentration, and puzzlement with insight all form a characteristic picture that should never be confused with hysterical or melancholic phenomena, which, unfortunately, is often the case. I have not mentioned the above matters from any critical angle, but merely to emphasize again the

importance of clinical observation and the ability to correlate one's findings. Furthermore, a warning may be incorporated to the effect that the use of electric convulsion therapy to remove what is called a depressive or emotional overlay is very questionable practice.

Finally, from the clinical standpoint attention may be directed to the large group of constitutionally predisposed persons who form the bulk of our mental hospital population. The origin and development of schizophrenic, affective, paranoid, and psychopathic states is as much a mystery to-day as it ever was, and little progress has been made in the prevention and control of the various forms of amentia. We may take a certain amount of encouragement from the genetic understanding of the transmission of Huntington's chorea, and from the interesting work of Penrose and Munro in this country and of Jarvis in the United States on the body–mind relationship which occurs in phenylketonuria. But a tremendous lot more requires to be done. The numbers of all such patients are increasing, hospital accommodation is inadequate, and our medical and nursing establishments are so curtailed that many of our patients are failing to get anything like the individual attention they need and deserve.

The above clinical situations which I have little more than mentioned show in no uncertain manner the vast territories which must be explored much more thoroughly. It is not a purely psychiatric matter, but one which calls for co-operative effort so as "to advance that knowledge which secures the development of the race, and establishes man's dominion over nature" (Laycock). My experience has taught me that the best psychiatrists are those who have acquired a sound, thorough training in general psychiatry and neurology before specializing in psychotherapy, psychoanalysis, child psychiatry, or forensic psychiatry. The great Charcot (his joints seem to have almost reached vanishing point) was an accomplished neurologist before he studied the manifestations of hysteria, and it has always impressed me that men like Freud, Meyer, White, Jelliffe, Ernest Jones, Putnam, Bleuler, and many others had had wide experience and training before embarking on their more specialized studies.

In any case, in this rich storehouse of the organic psychoses the diligent student, drawn from whatsoever sphere, will find infinite scope for his investigative spirit.

Medical Education

This takes me at once into the field of general medical education, which recently formed the subject of a World Conference. More specifically the relationship of psychiatry to medical education was discussed very fully at a conference organized in 1951 by the American Psychiatric Association and the Association of American Medical Colleges. The results of that conference are now available in book form under the able editorship of Whitehorn. The general formulation laid down is that the aim of all medical education—and especially of psychiatry—is "to prepare the medical student to deal intelligently and skilfully with patients as persons, and to provide him with the basic knowledge of psychological and social problems and resources in relation to health and disease."

In Edinburgh we have been able to put such a course into being. In the preclinical years an integrated course of instruction in psychology and psychiatry is given, dealing with such topics as the psychology of development and the life history of the individual; heredity and environment; temperament and character; personality structure; emotion and its role in symptom production. In the clinical years systematic and clinical lectures are given, and throughout the course emphasis is placed on out-patient work in the Royal Infirmary, Edinburgh. Psychiatry is one of the professional subjects which are obligatory in the final examination for the degree of M.B., Ch.B. During my teaching experience, both in Glasgow and in Edinburgh, large classes varying from 160 to 200 students annually have been the rule. While the students have not, therefore, had the close personal supervision which would be desirable, yet they have developed a keenness and an interest which have not made the professional examination an additional unwieldy burden. For my part I am convinced that the system in being has been of immense benefit both to the student and to his teachers. Furthermore, the establishment of professional or degree examinations in psychiatry puts the subject on an equality with other major subjects and ensures that the professor has his rightful place in the faculty of medicine.

While I am on this topic I might mention that universities as well as big industrial concerns are vitally concerned with wastage turnover, which in this instance centres in the unsatisfactory student. It is too often forgotten that when students come to their universities they are at a most vulnerable period of their development, so that the promise of their earlier years may, tragically often, not be fulfilled. We have a duty surely in our universities to promote mental hygiene, and to have the facility through our various departments to make the thorough personal and environmental inquiries which may preserve health and promote efficiency. This could be facilitated if it were more generally accepted that psychiatric units should be established as an integral part of every large general hospital. A fair suggestion is that from 5 to 10% of general hospital beds should be provided for psychiatric cases. It is lamentable to reflect how in this Welfare State we lag so far behind what has been accomplished so successfully in the United States, Scandinavia, and Germany.

The same suggestion or argument applies even more cogently to the affiliation of departments of child psychiatry to paediatric hospitals. Here again one can take a lesson from our American and Scandinavian colleagues, and can do more than pay lip-service to the slogan that childhood is the golden period for mental hygiene. We can and should provide accommodation for such children—not in mental hospitals, but in specially appointed clinics where they can have the benefit of all that present-day medicine can provide.

Much of what I have said in regard to undergraduate training and the affiliation of psychiatric clinics with paediatric and general hospitals holds good in relation to post-graduate and general-practitioner training. My experience is that both groups desire much more instruction and training in the principles of psychological medicine. Their success in practice depends on it. There are, of course, some doctors who state, blatantly enough, that they have no use for psychiatry, that psychiatrists should be avoided like the plague, that the subject is too mystical, theoretical, and dangerous, that it puts far more wrong ideas into the patient's mind than it removes. But in contrast to those cynics and sceptics there are an increasing number who are genuinely interested and who appreciate its significance in the medical hierarchy both as a specialty and as part of the working equipment of the general practitioner. Elaborate courses of instruction are by no means necessary, but familiarity with the ordinary methods of psychiatric examination are necessary, and an elasticity of mind which will allow him to switch to the possibility of a psychological explanation instead of seeking, long and vainly, for that pathological focus which is going to solve all the mystery.

The Art of Case-taking

What are those ordinary methods of psychiatric examination which have been referred to? The answer is quite simple—the art of case-taking. It may sound very unspectacular, but it is really fundamental for the whole of medicine, and I believe that it is in this field that psychiatry has made one of its greatest contributions. To do justice to any case it is essential to have a comprehensive life-study embracing hereditary structure plus environmental circumstances of a personal, social, or economic nature which may have influenced bodily or psychological development. It is dangerous practice to base our diagnosis and treatment on the symptoms alone, because the really important thing is the way the patient feels about them, and the setting or background in which they occur. It is diathesis and constitution we need more knowledge about, and how the

particular individual reacts to and compensates for the various bodily and psychological disabilities from which he may suffer. Selye applies the same concept to organic bodily states. That is why personality studies are so important, as in the differentiation of types as described in the first place by Hoch and Amsden, and, later, notably by Bleuler, Kretschmer, and Sheldon.

Such chronological studies, in terms of life history, are infinitely more illuminating than the cross-section method of the general physician. The latter uses the presenting symptom as his starting-point, and, while skilfully tracing out its ramifications, far too often fails to pay attention to the background, personal or environmental, in which the symptom is occurring. Cabot has given many examples of the fallacy of that method. It is a fault of training, a relic of a too concentrated, mechanistic objective approach, a vain seeking for a specific cause. How seldom we find it, and how much better it is to deal with all the multiple causative factors which may be playing a part. Then we will become much more accurate in our diagnosis, prognosis, and treatment. Very modestly it is suggested that our psychiatric case-taking methods may be of considerable value to our general medical colleagues. They will help them to remember that physical symptoms are often purely a face-saving device to maintain the *amour propre* of the patient. If this is forgotten, then examinations and treatment are introduced which often obscure the clinical picture. This, as I have said already, can be obviated by good history-taking and careful clinical evaluation. If the procedure I advocate was adopted we would hear much less of the failure of orthodox medicine and of the success of the medically untrained.

Our understanding of illness would be greatly increased if the relationship between the doctor and the social worker was drawn a bit closer. The social worker is not used intelligently enough. Social work is not a matter of almsgiving, of arranging loans, of giving financial or other material assistance. But it is the social worker's ability to size up a situation, to sense the atmosphere of the case, and to establish a good liaison between patient and employer, which is one of the most potent factors in successful rehabilitation and preventive medicine. We medical people do not appreciate how much we could gain, and how much more our patients would benefit, if we worked directly with the social workers rather than through the intermediation of the ward sister.

While, therefore, I have been striving to indicate the fields in which all medically trained people may learn to work more co-operatively, yet my main theme has been to show how psychiatry can be more greatly developed in relation to general practice. It is the psychologically oriented general practitioner who can become a much more important force in dealing with the great majority of nervous and mental ailments. The College of General Practitioners, which has just been founded, may be willing to consider how such a development can be most successfully pursued.

Conclusion

To conclude, I might make the following general suggestions:

1. A wider concept of medical education, so that all universities and medical schools recognize that the understanding and treatment of nervous and mental disorders is a matter of paramount national importance and should constitute a major subject in the medical curriculum.

2. Psychiatric clinics for in-patients and out-patients should form an integral part of all large general and paediatric hospitals.

3. Far greater reciprocity and co-ordination should be effected between all groups of medical men and social workers, in the hope that psychiatry will become less of a specialty and more part and parcel of general medicine.

TREATMENT OF RENAL OEDEMA WITH DEXTRAN

BY

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The obstinate oedema characteristic of type II nephritis (nephrosis, nephrotic syndrome, or chronic parenchymatous nephritis) is often difficult to treat. Limitation of salt and fluids seldom does more than mitigate the condition, and often not even that; the attempt to raise the level of albumin in the plasma with a diet rich in protein is equally unsatisfactory. Among the diuretics, only mersalyl is likely to be outstandingly successful. Even when circumstances appear favourable for administration of mercury—that is, absence of haematuria, normal renal-function tests, and normal blood pressure—many physicians are reluctant to use it in the presence of Bright's disease. More recently, ion exchange resins, A.C.T.H., and cortisone have been used. From the literature the response to these substances appears to be inconstant and the resins are difficult to stomach. The last resort is the removal of oedema by acupuncture or by the insertion of Southey's tubes at the ankles. With the introduction of antibiotics this procedure carries less risk of infection than formerly, but remains an unpleasant one.

Attempts to increase the colloid osmotic pressure of the plasma other than by high protein diet are not new. One of the earliest was by the intravenous injection of 6% gum acacia in normal saline, which was successfully used in the treatment of wound shock in the first world war. As a diuretic, this substance administered in 5% glucose achieved a measure of success, but became unpopular when experiments on animals showed that it remained in the tissues for years, deposited particularly in the liver, where it was said to depress the formation of plasma albumin. Later, blood and plasma were used, usually with little or no diuretic effect. With concentrated plasma, preferably with concentrated human plasma albumin, some diuresis is obtained. These latter blood products are expensive (concentrated plasma albumin is not obtainable in this country), and there is some risk of hepatitis in their use.

More recently the search for a substitute for plasma capable of restoring blood volume in patients suffering from shock has led to the use of gelatin, polyvinylpyrrolidone, and dextran. The last-named has been used as a diuretic in the treatment of renal oedema, and it is this aspect of its use with which this paper deals.

Dextran is a polysaccharide formed by the condensation of the glucose moiety of sucrose by the action of the organism *Leuconostoc mesenteroides*. Commercial dextran is prepared by the controlled hydrolysis and fractional precipitation of this crude dextran. It is thus theoretically possible to produce a dextran of any desired molecular weight, but, in practice, a fairly wide scatter in molecular size results, and it is so far practicable only to make preparations in which a large proportion of the molecules are within the chosen range of molecular size. Not only does the dextran made by

different drug firms vary in molecular distribution, but it is probable that different batches made by the same firm are not identical.

Dextran was introduced in Sweden by Grönwall and Ingelman (1944), who tested its properties in animals, and later in man (1945). They pointed out that an ideal substitute for plasma should be non-toxic, non-antigenic, and either completely excreted or completely metabolized—that is, it should not be stored in the tissues. They considered dextran to have these properties. Bohmansson, Rosenkvist, Thorsén, and Wilander (1946) confirmed the work with large-scale trials in which each batch of dextran was tried first on patients in the last stages of carcinoma. For some years dextran has been used extensively in Sweden for the treatment of shock, and Thorsén (1950) estimated the incidence of reactions to be as low as 0.1%. Bloom (1951) did not find any reactions in 51 patients suffering from shock, or in 50 others who were not suffering from shock.

On the other hand, Turner, Butler, Smith, and Scudder (1949), in America, observed reactions in 10 out of 30 patients. These reactions took the form of fever, headache, and tachycardia, with urticaria in six instances, cyanosis three times, and dyspnoea once. None of their patients was suffering from shock, but 500 ml. of 6% dextran was given in the short time of 30 minutes. More recently, in this country, Maycock (1952) noted reactions in only 1.51% of 1,647 patients who had received dextran at various medical centres, mostly to combat shock. There was one death, in a moribund patient, and the relationship to dextran was uncertain. Pyrexia, headache, urticaria, and pain in the loins and other abnormalities were noted. A severe reaction developed in one patient but none at all in 46 others who received infusions of the same batch of dextran. Accordingly, Maycock thought reactions possibly occurred as a result of sensitization to *L. mesenteroides* or antigenetically related organisms such as pneumococcus type 2 or 20. As Maycock states, it should never be forgotten that large numbers of infusions have been given in the treatment of shock without any reaction whatever.

The fate of injected dextran is still being intensively studied. Thorsén (1949), after infusion into animals of an amount equivalent to one-third of the body weight, found by examination of watery extracts no dextran in the liver, spleen, bone marrow, brain, lungs, heart muscle, or kidney, and observed no morphological changes. On the other hand, Turner and his coworkers (1949) found minimal but in their view irreversible changes in the liver, spleen, kidney, and reticuloendothelial system. These took the form of giant-cell formation and proliferation. Goldenberg, Crane, and Popper (1947) and Hartman (1951) also noted histological changes in the kidney, the liver, and the reticuloendothelial system, but considered them to be probably reversible. Using rabbits, to which the equivalent of 1.5 litres of 6% dextran was given daily for seven days, Bull and his colleagues (1949) detected dextran by chemical methods in spleen and lymph nodes up to 21 days later. With a serological method, dextran was found to be still present up to 56 days afterwards.

The amount of dextran excreted in the urine varies considerably with the molecular distribution of the product used. Recent experimental work has shown that up to 40%, presumably of small molecular size, is excreted in the urine—mostly in the first 24 hours and the rest in four to six days. Dextran has also been found in the faeces. Some of the remainder is metabolized, as shown by Gray, Siiteri, and Pulaski (1951), who found the D : N ratio arose when dextran was given to phloridzinized dogs. Work with dextran containing radioactive carbon indicates that some dextran is taken up by the reticulo-endothelial system. It therefore seems highly probable that this fraction also is eventually broken down and metabolized. Some tagged carbon is lost in expired air (Pulaski, 1952).

It is noteworthy that dextran has been approved by the Federal Food and Drug Administration, and that doctors of the American Forces have been authorized to use it wherever they believe it may be suitably employed in place of plasma (Government Services, 1953).

The objects of our investigation were (1) to confirm that dextran is a safe and efficient diuretic for relief of renal oedema ; (2) to attempt to determine the influence of the size of the dextran molecule upon diuresis ; and (3) to study some of the biochemical changes.

Clinical Material and Plan of Treatment

Dextran was given on 81 occasions to eight patients, all of whom showed oedema of long duration, heavy albuminuria, and marked hypo-albuminaemia. Full clinical data are given in the case histories. Throughout the period of treatment the patients were kept in bed and received a constant diet containing less than 2 g. NaCl and a fluid intake of 1,200 or 1,800 ml. in 24 hours. The protein intake in one patient was 60 g. daily, in the others either 100 or 120 g. No other treatment was given. Collections of urine were made over periods of 24 hours, and the patients were weighed daily as a further check on fluctuation in oedema. Dextran was not given until it was reasonably certain that diuresis from the effects of diet or rest in bed was not taking place.

During the period before administration of dextran, observations were made on the protein and cholesterol of the serum, on the blood urea and urea clearance, and on the haemoglobin and packed cell volume. Where possible these observations were repeated at regular intervals.

Salt-free dextran was used, much of which was presented to us by Benger Laboratories Ltd. 540 ml. was given by intravenous infusions over a period of not less than four hours. A shorter infusion period was found to be associated with a greater liability to severe headache, nausea, and vomiting. Five infusions were given on consecutive days to Cases 1–6, but in one instance the fifth infusion was omitted altogether because severe dyspnoea occurred after the fourth. Another patient received only 220 ml. at the fourth and fifth infusions (without any reaction), because severe headache had developed after the third. Cases 7 and 8 received single infusions of 540 ml. in order to study more closely the fate of the injected dextran.

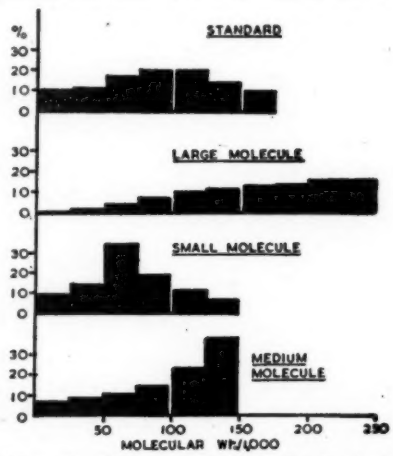

FIG. 1.—Molecular weight distributions of the preparations of dextran used.

Four categories of dextran were used ; the standard commercial salt-free preparation in 6% strength and three preparations of differing molecular distribution (Fig. 1). These

were designated for convenience large, medium, and small molecule, according to the predominant molecular size in each. All were salt-free and were of 10% strength.

Results

Diuresis.—Increase of urinary output was produced by every course of dextran. Outstandingly good results were obtained in Cases 1–3, which became at least temporarily free of oedema, losing 12.3, 13.6, and 18.2 kg. body weight respectively within 7–14 days. On recurrence of oedema, a further course of dextran was again followed by diuresis. In Case 4 a moderate diuresis was produced on five occasions although the patient was never free of pitting oedema. Results in Cases 5 and 6 were less striking, but it is fair to say that in neither was the degree of oedema at all comparable with that present in the other four (Table I). In

TABLE I.—*Effect of Dextran on Oedema*

Case No.	Preparation of Dextran	Weight Loss (kg.)	Weight before Start of Treatment (kg.)	Duration of Diuresis (Days)
1	Standard 6%	12·3	64·5	9
	" "	3·2	60·9	8
2	" "	13·6	92·3	7
	" "	6·4	83·6	6
3	Large molecule 10%	18·2	65·9	14
	Medium " "	10·9	65·9	5
4	Standard 6%	6·4	70·5	9
	Large molecule 10%	7·7	64·5	19
	Medium " "	8·2	69·1	11
	Large " "	6·4	69·5	22
	Small " "	5·9	70·9	6*
5	Large " "	2·7	59·5	13
	Medium " "	4·1	65·6	6
6	Medium " "	2·7		5

* Four infusions only.

Case 7 the administration of a course of small-molecule dextran was begun the day after an apparently spontaneous increase in the output of urine, and the data are therefore excluded from the assessment of dextran as a diuretic.

Effect of Molecular Size of Dextran on Diuresis.—Diuresis occurred with every preparation of dextran irrespective of whether the concentration was 6 or 10%, or whether large or small molecules predominated in the preparation used. With the method of administration employed and the number of observations made, it was not possible to say that one preparation produced a greater loss of oedema

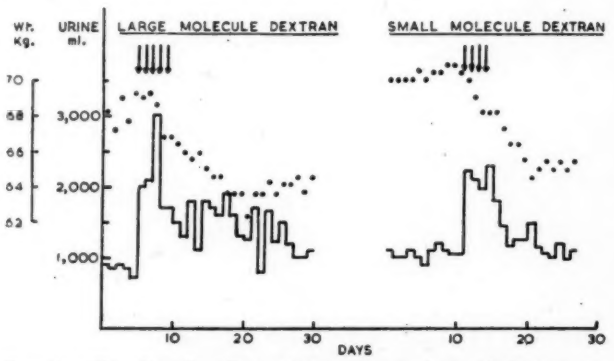

FIG. 2.—The diuretic effect of two preparations of dextran on Case 4.

than another (Table I). It is clear, however, that the diuretic effect of large-molecule dextran is of longer duration than any of the others (Table I). The duration of diuresis with large- and small-molecule dextran in the same patient is shown in Fig. 2. The biochemical findings are in harmony with these clinical observations, which suggest that the larger molecules remain longer in the blood stream.

Effect of Dextran on the Course of Nephritis.—Dextran is an effective agent for dispelling oedema, but its effect is temporary, and there is no evidence that it favourably affects the course of the disease in any other way. On the other hand, three patients (Cases 1, 3, and 6) have died of uraemia 54, 24, and 24 weeks respectively after the last infusion of dextran. In two of these patients the urea clearance was subnormal before the start of treatment. Two were suffering from amyloidosis of the kidneys, a progressive fatal lesion. Periodic observations on renal function for some months after dextran showed nothing to suggest that deterioration was due to its administration, and in our view death occurred in the natural course of the disease and was not accelerated by dextran.

Toxic Effects

Some form of side-effect was shown after most of the infusions, but seldom were there symptoms which gave rise to concern. In Case 4, on the conclusion of the fourth infusion of small-molecule dextran, shivering, marked dyspnoea, and cough developed. The patient complained of nausea and had a temperature of 100.4° F. (38° C.). On examination there were only scanty rales at the lung bases and no wheezing was heard. He was not cyanosed. The blood pressure remained unchanged. The pulse was poor in quality and the rate was 124 per minute. Within four hours these manifestations passed off. This patient had received four courses of dextran (Table I) over 11 months, but there had been an interval of four months since the last course. Accordingly, a skin test was carried out with dextran before the infusion. It was negative. A similar but less severe side-effect occurred in Case 7 during the infusion of small-molecule dextran, which was stopped after 340 ml. had been given.

After the earlier infusions, severe headache lasting for six or more hours was noted. Nausea and vomiting were less common. In one patient a subconjunctival haemorrhage developed and in another bleeding from the gums and nose occurred. Rashes were not seen. These side-effects were less frequent and less severe when the infusion was given more slowly—that is, not faster than four hours for 540 ml. It was not possible to correlate their occurrence with the molecular size of the product used; but it is worth mentioning that the sharpest fall in packed cell volume and in haemoglobin, indicating the greatest increase in blood volume (61%), was seen in association with the severe reaction in Case 4 after administration of small-molecule dextran. Blood-pressure readings before, during, and after infusion showed no change in our cases, but we have not given dextran to anyone with appreciable hypertension.

In two patients hepatic enlargement of two to three fingerbreadths below the costal margin was detected immediately after a course of dextran. This disappeared in two to three weeks, and at necropsy in Case 3 (dying of uraemia six months after administration of dextran) histological observations showed no evidence of damage and, with the method used, no evidence of dextran. We were at this time unaware of the special method required for the detection of dextran advocated by Mowry, Longley, and Millican (1952). This observation would seem to be in agreement with reports of the temporary deposition of dextran in various organs. The absence of other signs of cardiac failure make it unlikely to have been due to engorgement.

Biochemistry

Changes in Blood Volume as Reflected by Changes in Haemoglobin and Haematocrit

Since it was impracticable to make frequent estimations of the blood volume, observations on haemoglobin and haematocrit were made before and at intervals after the administration of dextran. It was thought unlikely that alterations in the total circulating haemoglobin as a result of marrow influence would occur over short periods, and consequently that changes in the haematocrit and haemoglobin level would provide an index of change in the blood volume.

TABLE II.—*Behaviour of Haematocrit and Haemoglobin Levels after Infusion of Dextran*

Preparation of Dextran	No. and Volume of Infusions	Case No.	Haematocrit %				Haemoglobin, g. per 100 ml.			
			Before Dextran	½ Hour After First Infusion	20 Hours After First Infusion	20 Hours After Last Infusion	Before Dextran	½ Hour After First Infusion	20 Hours After First Infusion	20 Hours After Last Infusion
Large molecule	5×540 ml.	3	36·0	26·0	—	27·0	12·2	8·9	—	9·1
	5×540 „	3	32·0	—	25·5	21·0	10·2	—	8·3	6·7
	5×540 „	4	28·5	22·0	25·5	—	10·8	8·4	9·6	—
	5×540 „	4	26·5	21·5	—	19·0	9·6	7·9	—	6·8
	5×540 „	5	38·0	33·5	—	29·5	12·0	11·1	10·4	9·7
	1×540 „	7	34·0	25·0	29·0	—	9·8	7·2	8·5	—
Medium molecule	5×540 „	4	37·0	28·0	29·0	25·0	11·8	10·4	11·0	9·0
	5×540 „	5	35·0	—	32·0	30·0	11·1	—	10·7	9·5
	5×540 „	6	44·5	39·0	42·0	40·0	13·9	12·2	12·6	12·8
Small molecule	4×540 „	4	38·0	26·0	28·5	23·5	12·8	9·0	10·2	8·0
	1×540 „	7	43·0	32·0	36·0	—	15·4	11·6	13·0	—
	1×340 „	7	41·0	33·0	38·0	—	15·0	11·8	13·4	—
	1×540 „	8	37·0	28·0	31·0	—	11·2	8·4	9·6	—
	1×540 „	8	32·5	26·5	31·0	—	9·8	7·4	9·6	—

A considerable increase in blood volume was apparent immediately after the first infusion of 540 ml. of dextran, the degree of this increase varying from 13 to 46%. By the following morning a considerable reduction had taken place (Table II). With repeated daily infusions further increases tended to occur and the maximum fall in haemoglobin and haematocrit was usually noted after the final infusion. In general, the rise in plasma dextran was proportional to the fall in haemoglobin and haematocrit. No exact correlation could be determined between them and the preparation of dextran used. However, to Case 4, courses of all four were given and the fall produced by the small-molecule preparation was much the greatest (Table II). It was calculated that the blood volume increased by 61% in this instance, the highest value in the series. The first three cases received 6% commercial dextran. Observations were not made on the haemoglobin and haematocrit; but it is clear that a sharp increase in blood volume also took place as shown by the fall in serum protein. On two occasions restoration of the haemoglobin and haematocrit to the pre-dextran levels lagged behind the rise in serum protein. This was particularly noticeable in Case 4.

Serum Protein.—The serum protein levels showed a sharp drop within half an hour after an infusion of dextran, with gradual return to normal over seven or more days.

Serum Cholesterol.—A striking fall in serum cholesterol was observed within half an hour after the injection of dextran. When considered in relation to the fall in serum protein (Table III) it would seem reasonable to accept this

TABLE III.—*Behaviour of Serum Cholesterol After Infusion of Dextran*

Case No.‖	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.	Serum Cholesterol mg./100 ml.	Serum Protein g./100 ml.
	Before Dextran		*20 hours after 5th infusion*		*Proteins near pre-infusion level*	
3	926	—	204	—	—	—
3	675	3·5	245	1·25	—	—
4	310	4·0	100	1·5	155	4·0
4	235	4·0	114	1·25	159	3·5
4*	316	5·5	92	2·2	177	4·5
5	260	4·5	108	2·0	220	4·5
5	—	5·5	122	2·5	176	5·5
			20 hours after 1st infusion			
7	640	4·25	400	2·8	450	4·0
7	412	4·5	268	3·1	176	4·5
7†	400	5·0	285	3·0	380	4·5
8	175	6·0	110	4·0	134	5·5
8	188	5·75	118	4·0	—	—

* Only 4 infusions. † Only 340 ml.

as further evidence of dilution due to increase of plasma volume. However, even a week or more after the infusion of dextran, when the serum protein had returned to pre-infusion level, the serum cholesterol was usually still well below its original value.

Plasma Dextran.—Values noted 20 hours after the infusion of 540 ml. of 10% dextran ranged from 0.7 to 1.2 g./100 ml. Too few observations were made, however, to determine whether differences could be correlated with the preparations of dextran employed. On subsequent days the values fell more rapidly in those patients who had received small-molecule dextran. When a course of five daily infusions of large-molecule dextran was administered the plasma levels after the final infusion ranged from 2.4 to 3.7 g./100 ml. Fourteen days afterwards plasma levels of 1.2 and 1.3 g./100 ml. were found in Case 3 on two occasions. Only one patient received a course of small-molecule dextran and this was stopped after four infusions of 540 ml. because of a severe reaction. The level of dextran in the plasma was then 1.7 g./100 ml.

Urinary Dextran.—Table IV shows the difference in the amount of dextran excreted in the urine when single infusions of large- and small-molecule dextran were given.

TABLE IV.—*Excretion of Large- and Small-molecule Dextran in the Urine (g. per day)*

Days after Infusion of 540 ml.	Large Molecule		Small Molecule	
	Case 7	Case 8	Case 7	Case 8
1	4·6	1·3	14·8	9·6
2	—	0·8	8·1	1·9
3	2·2	0·7	1·6	1·8
4	1·5	0·5	0·9	0·7
5	1·1	0·5	0·9	0·8
Cumulative ..		3·8	26·3	14·8

While there is no point in comparing these results with the theoretical loss in patients with intact kidneys, it is clear that excretion of dextran is much greater when a preparation containing a high proportion of small molecules is used. The fact that Case 7 excreted 26.3 g. in five days and Case 8 only 14.8 g. in the same period, although both had received small-molecule dextran, may possibly be explained by a difference in the nature of the lesion, the former being an example of type II nephritis and the latter of amyloid nephrosis. The greater excretion of small-molecule dextran was also demonstrated in Case 4, who, in the week following four daily infusions of the small-molecule preparation, excreted 112 g. (52%), whereas only 33 g. (12%) was excreted in a similar period after five pints (2.8 litres) of the large-molecule product.

Case Histories

Case 1.—A woman aged 21 developed oedema of her legs two years before admission to Stobhill Hospital on November 6, 1951. There was no history of preceding infection. On examination oedema was found to be general and the urine contained much albumin; but only scanty casts and red blood corpuscles were found. Serum protein was 4 g./100 ml., serum albumin 1.8 g./100 ml., and serum choles-

terol 552 mg./100 ml. Blood urea was normal (22 mg./100 ml.), but urea clearance was 35% of average normal. Blood pressure was 120/80 mm. Hg. Fundi were normal. The heart, lungs, and nervous system showed no abnormality. Some ascites was present. On a diet rich in protein and poor in salt there was no improvement; but after a course of dextran massive diuresis took place. Oedema gradually reaccumulated and a second course of dextran was again successful. She was discharged improved on December 21. Her urea clearance three months later was 36%. About six months after dismissal renal function began to fail sharply, and she died in her own home on November 29, 1952, of uraemia.

Case 2.—A man aged 34 developed a sore throat in October, 1950, followed a week later by swelling of his feet. When admitted to Stobhill Hospital on January 10, 1951, there was marked general oedema. Blood pressure was 160/112 mm. Hg. The fundi were normal. The urine contained much albumin and numerous hyaline and granular casts. Red blood corpuscles were present, but in numbers too few to give a positive guaiac reaction. The heart, lungs, abdomen, and central nervous system showed no abnormality. Ascites was present. Serum protein was 4.5 g./100 ml., serum albumin 1.6 g./100 ml., and serum cholesterol 384 mg./100 ml. The blood urea was 42 mg./100 ml. and the urea clearance 57%. His condition remained substantially unchanged for 14 months in spite of diet, mersalyl, urea in large doses, A.C.T.H., cortisone, ion-exchange resin, and insertion of Southey's tubes in the legs. Profuse diuresis followed each of two courses of dextran, and he was discharged from hospital much improved in February, 1952; his blood urea being then 35 mg./100 ml. and the urea clearance 72%. Renal function since then has remained good (urea clearance 70% on January 10, 1954) and the blood pressure unchanged.

Case 3.—A woman aged 43 developed oedema insidiously 11 months before admission to Stobhill Hospital on May 2, 1952. For six months ascites had been present. Six years previously she had had pre-eclamptic toxaemia and labour had to be induced at seven and a half months. Eighteen months later there was a normal delivery, and during this pregnancy the urine remained free of albumin and the blood pressure did not rise above 160/110 mm. Hg. On examination in May, 1952, she showed generalized oedema and ascites. In the urine there was much albumin; casts were numerous; but there were no erythrocytes. Serum protein was 4 g./100 ml., serum albumin 1.2 g./100 ml., serum cholesterol 860 mg./100 ml., blood urea 32 mg./100 ml., urea clearance 45%. Blood pressure was 105/85 mm. Hg. The fundi were normal. The heart, lungs, and nervous system showed no abnormality. No improvement followed a protein-rich salt-poor diet. After a course of dextran 18.2 kg. of body weight was lost in 14 days and she was discharged on May 21. On July 5 she was readmitted because of massive oedema. Her serum protein level was 3.5 g./100 ml., albumin 0.8 g./100 ml., blood urea 47 mg./100 ml., and urea clearance 47%. Diuresis again followed a course of dextran. On the day after the fifth injection the liver was noted to be three fingerbreadths below the costal margin and very firm. The serum bilirubin and prothrombin time were within the normal range: the thymol turbidity was two units and the thymol flocculation test negative. When discharged, at her own request, 14 days later the liver was then only just palpable. Renal function was unchanged. She died of uraemia on January 27, 1953. The findings at necropsy were unexpected. There was marked amyloid disease of the kidneys and a large area of necrosis in the cortex of one. No gross or histological evidence of damage due to dextran was made out in the liver, spleen, or kidneys, nor could any focus of sepsis be found except a degree of sinusitis.

Case 4.—A man aged 44 noticed oedema of the legs a month before admission to hospital in December, 1951. There was no history of preceding infection. On examination there was widespread oedema. The urine contained much albumin but only a few red blood corpuscles and casts. Blood pressure was 120/90 mm. Hg. The fundi were normal. Serum protein was 4.8 g./100 ml., serum albumin 1.5 g./100 ml., serum cholesterol 235 mg./100 ml., serum urea 45 mg./100 ml., and urea clearance 33%. The heart, lungs, abdomen, and nervous system showed no abnormality. This patient received no relief from diet. Five courses of dextran were given, each of which produced considerable diuresis, but never enough to make him free of oedema. Renal function was unchanged during the six months he was receiving the first four courses, but is gradually deteriorating: blood pressure 170/110 mm. Hg and blood urea 134 mg./100 ml. on September 15, 1953.

Case 5.—A man aged 49 had suffered from pulmonary tuberculosis for at least five years. In January, 1952, he was admitted to hospital with erysipelas, and a month later swelling of the legs was noted. When admitted to Stobhill Hospital in April there was oedema of the legs only. The urine contained much albumin and many granular casts, but no red blood corpuscles. The blood pressure was 110/60 mm. Hg. The fundi were normal. Serum protein was 5.5 g./100 ml., serum albumin 1.6 g./100 ml., serum cholesterol 350 mg./100 ml., blood urea 47 mg./100 ml., and urea clearance 54%. The heart, abdomen, and nervous system showed no abnormality. There was dullness over the left lung, with deficient respiratory murmur. No adventitious sounds were heard. The trachea was deviated to the left. A skiagram showed collapse of the left lung and a small effusion. At this time no tubercle bacilli were found in the sputum. The fingers showed marked clubbing. A diagnosis of amyloid nephrosis complicating pulmonary tuberculosis was made. With dextran a moderate diuresis which caused reduction in oedema was induced on two occasions. On September 15, 1953, the serum protein was 5.5 g./100 ml., serum urea 37 mg./100 ml., and urea clearance 71%. His condition remains stationary.

Case 6.—A man aged 50 was proved to have pulmonary tuberculosis in 1944. For three months before admission in April, 1952, swelling of the legs had been noted. On examination oedema was found to be moderate only, and confined to the legs. Albuminuria was profuse and casts and erythrocytes were scanty. The blood pressure was 140/85 mm. Hg. The fundi were normal. The heart, abdomen, and nervous system showed no abnormality. There was marked clubbing of the fingers. Over the right upper chest there was extensive dullness, with areas of bronchial respiratory murmur and rales. A skiagram showed cavitation and fibrosis. No tubercle bacilli were found in the sputum at this time. Serum protein was 6 g./100 ml., serum albumin 2 g./100 ml., serum cholesterol 335 mg./100 ml., blood urea 30 mg./100 ml., and urea clearance 90%. A diagnosis of amyloid nephrosis complicating pulmonary tuberculosis was made. Dextran produced slight diuresis. Five months after his discharge from hospital on May 16, 1952, renal function rather suddenly deteriorated and death occurred from uraemia. The clinical diagnosis was confirmed at necropsy.

Case 7.—A boy aged 14 developed generalized oedema in January, 1953, without preceding infection other than boils on the face. When seen on February 20, 1953, he had moderate oedema of the legs and sacrum. The fundi were normal; blood pressure was 130/75 mm. Hg. The heart, lungs, and nervous system showed no abnormality. In the urine there was much albumin; a few granular casts and erythrocytes were found. Serum protein was 3.5 g./100 ml., serum albumin 2 g./100 ml., serum cholesterol 462 mg./100 ml., blood urea 34 mg./100 ml., and urea clearance 56%. When he was last seen his condition was unchanged.

Case 8.—A man aged 62 was admitted to hospital on April 14, 1953, complaining of swelling of the legs and abdomen for two weeks. For many years previously he had had a productive cough which had become worse in the past year and was associated with loss of weight. On examination he was emaciated, but showed gross generalized oedema and also ascites. There was very marked clubbing of the fingers.

In the sputum tubercle bacilli were numerous. The upper zone of the right lung was dull and the breathing bronchial. Rales were numerous and a skiagram confirmed the presence of cavitation. The heart and nervous system showed no abnormality. Blood pressure was 140/80 mm. Hg; the fundi were normal. After withdrawal of 2,700 ml. of fluid from the peritoneal cavity, the liver and spleen were not felt. In the urine there was a large amount of albumin but no casts and no erythrocytes. Serum protein was 5.5 g./100 ml., albumin 1.2 g./100 ml., serum cholesterol 168 mg./100 ml., serum urea 37 mg./100 ml., and urea clearance 37%. A diagnosis of pulmonary tuberculosis complicated by amyloidosis was made. There has been little change in his condition.

Discussion

An earlier publication by Wallenius (1950) indicated that dextran was a diuretic for nephrotic oedema. While Olive, Mills, and Lundy (1953) achieved good results in 7 out of 12 children, Bedford and Broughton (1951) had no success in three attempts on one patient. Both Wallenius (1950) and Olive and co-workers (1953) suggested that single injections are of little or no value.

When we gave five infusions of 540 ml. of 10% dextran on consecutive days, three out of six patients were rendered free of oedema and three were improved. In one instance dextran was successful after a wide variety of measures, including ion-exchange resin, A.C.T.H., cortisone, and even Southey's tubes, had made little impression. The good result was temporary in every instance, but a further course of dextran was again satisfactory on all of 11 occasions. We have found dextran to be consistently effective, and consider it to be a powerful diuretic which is valuable when other measures fail. It is perhaps particularly useful when it is decided not to use mersalyl.

Concerning the mechanism of this diuresis we have little to say. In the treatment of shock the object of administering dextran is to restore the blood volume by infusion of a substance which will remain in the vascular system for a long period. In patients suffering from type II nephritis with hypoproteinaemic oedema, the increase of osmotic pressure of the plasma due to the circulating dextran draws oedema fluid from the tissues into the blood stream. Similar changes followed the intravenous injection of acacia, a plasma volume expander of the first world war, which had a short vogue as a diuretic in nephrotic oedema (Lepore, 1937). Peters (1935) linked increase in blood volume after acacia with the production of diuresis, and, while the mechanism of this is still not understood, more recently MacArthur (1946) found that increase of blood volume was associated with the onset of spontaneous diuresis in nephrotic children. Marked haemodilution without diuresis was observed in the case reported by Bedford and Broughton (1951), who attributed this to the poor state of renal function. None of our cases is comparable with their case in that respect.

When the dextran is excreted or leaves the blood stream the blood volume returns to normal, as shown by the return of the haematocrit, haemoglobin, and total plasma protein to pre-infusion levels. The diuretic effect is therefore of limited duration.

Boyd, Fletcher, and Ratcliffe (1953) showed that dextran containing a high percentage of small molecules left the blood stream more rapidly than a product with a high percentage of larger molecules. The loss occurred into the urine and also, it was stated, into the interstitial fluids. There is not yet general agreement concerning the optimum molecular size to promote diuresis. Wallenius postulated that a preparation of small molecules might prove to be more effective, as they are osmotically more active, and, since they pass freely into the urine, they might also promote diuresis by hindering tubular reabsorption of water. Yet he held that they might pass more freely into the tissue spaces and there exert osmotic pressure against the plasma protein and circulating dextran. This we have not confirmed, in so far as no dextran was detected on examination of oedema fluid. Bedford and Broughton (1951) also failed to find dextran in oedema fluid, and made the point that it may be present in too great dilution to be detected.

A preparation of larger and consequently less osmotically active molecules would, on the other hand, remain longer in the blood stream and so might produce a greater total diuresis. With the preparations used we were, however, unable to detect any material difference in the amount of oedema lost even when the three preparations were given to the same patient with a comparable degree of oedema as judged by body weight.

The findings of this paper cannot easily be compared with those of Wallenius (1950) or of Olive and his co-workers (1953), since both used dextran prepared by Pharmacia, of Sweden, differing in molecular distribution from the dextrans used by us. There is no support from our results for the suggestion made by Wallenius that diuresis might be due to diminished reabsorption of water from the tubules in the presence of a large number of small molecules of dextran, since the diuretic effect was just as good with large-molecule dextran as with the small-molecule preparation.

Hazards of Dextran

The hazards may be considered under two heads. In the first place, those that develop during the period of infusion or very shortly afterwards. Reactions of this type, usually of mild degree, were seen in most of our patients. They included headache and nausea; vomiting and dyspnoea were less common. These, along with rashes and backache, have usually been attributed to sensitivity or to the large molecules of dextran. We are inclined to think, however, that most if not all of these side-effects occurring in patients with oedema are due to overloading of the circulation. We have also seen subconjunctival haemorrhage and bleeding from the gums and nose. Headache, at least, is certainly minimized if the dextran is given slowly. Severe reactions, causing concern, occurred twice, on both occasions when small-molecule dextran was given. The high incidence of reactions in our patients may be explained on the basis that a normal blood volume is suddenly much increased by the attraction of oedema fluid into the blood stream when the plasma osmotic pressure is raised by dextran. Consequently very slow administration is clearly advisable to minimize reactions, and the use of small-molecule dextran is best avoided.

The second potential hazard of dextran administration is the possibility of its retention in the tissues. For a time at least it appears to lodge in the reticulo-endothelial system, particularly of the liver and spleen, and we have twice observed that the haematocrit and haemoglobin values have not returned to the pre-infusion level along with the serum protein. In one patient there was a drop in haemoglobin of over 2 g./100 ml. which was not made good until two months after the dextran was stopped. We can only tentatively interpet this as an indication that marrow function may be temporarily impaired by dextran in some individuals. The evidence gradually accumulating is strongly in favour of the view that all dextran injected is eventually excreted or metabolized. In our work there was no evidence that renal function was adversely affected by its use.

Appendix: Analytical Methods

Haemoglobin, haematocrit, and plasma dextran levels were determined on heparinized blood.

Haemoglobin was estimated as oxyhaemoglobin by photoelectric colorimetry.

Plasma dextran was estimated in the first cases by the method of Hint and Thorsén (1947), but later samples were estimated by a method using anthrone and based on the work of Morris (1948). This method, which was found to give comparable results, was preferred because of its greater rapidity and simplicity. Urinary dextran was also estimated by this procedure.

Serum total protein was estimated by the biuret method. It has been widely reported that the biuret reaction gives falsely high results in the presence of dextran, since dextran combines

with copper in alkaline solution (Jacobsson and Hansen, 1953), but these same authors have pointed out that this occurs only when a method such as that of Lehmann (1944) is used in which there is no initial precipitation of the proteins.

As they have shown, and we have confirmed, the disturbing influence of dextran is, for practical purposes, eliminated by precipitating the protein with trichloracetic acid.

Serum cholesterol was estimated by the modification (King, 1951) of the method of Sackett (1925).

Summary

The diuretic action of dextran in renal oedema has been investigated and confirmed.

Attention is drawn to the large increases in blood volume produced in these patients by intravenous infusions of dextran.

Headache and nausea, usually of slight degree, occurred in most of our patients, and it is postulated that these symptoms were due to overloading of the circulation. Vomiting and dyspnoea were less frequent.

In an attempt to find the optimal molecular size of dextran to promote diuresis four preparations with differing molecular distribution were used. There was little difference in the amount of diuresis produced, but the most severe side-effects, accompanied by the greatest increases in blood volume, occurred after infusion of the preparation containing the greatest proportion of small molecules. The most prolonged diuresis was effected by the large-molecule dextran.

Attention is drawn to the fact that the presence of dextran does not interfere with the estimation of plasma proteins by the biuret reaction provided the proteins are first precipitated by trichloracetic acid.

We wish to express our thanks to Dr. Frank Fletcher, medical director of Benger Laboratories Ltd., who obtained for us three preparations of dextran and gave us the data in Fig. 1, and to Benger Laboratories Ltd., who provided the dextran gratis. We also thank Dr. J. W. Chambers, clinical biochemist to Stobhill General Hospital, in whose department much of the work was done, for his valuable help and encouragement.

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THROMBOCYTOPENIC PURPURA AFTER ADMINISTRATION OF GOLD

COMPARISON OF TREATMENT WITH DIMERCAPROL, A.C.T.H., AND CORTISONE

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Various authors, reporting on the incidence of toxic reactions to gold salts, record percentages varying from 20 to 77. Severe reactions occur in approximately 6%. Amongst the most serious are thrombocytopenic purpura, agranulocytosis, and aplastic anaemia. Hartfall *et al.* (1937), in a series of 750 cases of rheumatoid arthritis given gold, noted toxic reactions of greater or lesser severity in 40% of patients, which included nine cases of thrombocytopenic purpura. Three of these patients died. Wintrobe *et al.* (1939), in a review of the literature, reported seven cases of purpura, four of which were fatal. Cecil *et al.* (1942) recorded three cases of purpura, one fatal, in a series of 245 cases given gold. Price and Leichtentritt (1943), in a series of 101 patients, noted three with purpura, one of whom died. Short *et al.* (1946) reported one fatal case of purpura in a series of 47 patients. Nyström (1950) encountered one fatal case of purpura among 572 patients given gold. Mettier *et al.* (1948), on the other hand, recorded four cases of purpura among 160 patients, none of which were fatal. Various other workers have reported isolated cases, but the incidence of this complication of gold therapy has declined in recent years, presumably owing to a better appreciation of the dangers of gold administration.

The introduction of 2,3-dimercaptopropanol (dimercaprol, " B.A.L.") by Peters *et al.* (1947) as a therapeutic agent in the treatment of poisoning by arsenic and other heavy metals quickly led to its use in the treatment of toxic reactions due to gold. Many of the less serious reactions, such as dermatitis, rapidly improved following the use of dimercaprol (Ragan and Boots, 1947; Cohen *et al.*, 1947; Macleod, 1948; Montgomery, 1950; Edström, 1950; Kirsch, 1951). Good results have been recorded in cases of thrombocytopenic purpura, but only a few have been reported in detail. Lockie *et al.* (1947) describe a case of thrombocytopenic purpura due to gold which had shown no response to various methods of treatment over a period of three months and ultimately developed a subarachnoid haemorrhage. Dimercaprol was administered in doses of 180 mg. four-hourly for two days, then twice daily for ten days (total 5.7 g.), and the patient made a good recovery. The platelet level rose from 36,000 to 120,000 in three weeks, and was at approximately the same level three months later. Kroese (1949) described two cases of purpura following gold administration. In one case the response to dimercaprol was excellent. The drug was given immediately the symptoms appeared. The

second case was of five months' duration and showed no response to dimercaprol. Brodthagen (1950) reported one case in which 2 ml. of 5% dimercaprol was given daily for three days, but the patient died on the third day.

Initially dimercaprol was used mainly by intramuscular injection in the doses recommended by Peters *et al.* (1947). A course consisted of four injections, each of 2 ml. of 5% dimercaprol, at four-hourly intervals on the first day (400 mg.), followed on the second, third, and fourth days by 2 ml. twice daily. On the fifth and sixth days a single injection of 2 ml. was given (total dose 1.2 g.). In severely ill patients nearly double these doses were given, but "with considerable trepidation" (Longcope and Luetscher, 1946).

Only a small number of cases of thrombocytopenic purpura due to gold administration and subsequently treated with dimercaprol have been described in detail. In view of this it was considered important to report in full two further cases, in one of which the total amount of dimercaprol far exceeded the recommended dose, without ill effect.

Case 1

This patient, a man aged 49, was first seen as an outpatient in October, 1948. He had suffered from rheumatoid arthritis since 1946. He was treated conservatively until 1949, when a course of gold was recommended. Three days after the fifteenth injection (total 0.22 g.) a purpuric eruption appeared. He was admitted to hospital two days later.

On admission there was evidence of a recent epistaxis with haemorrhagic bullae present on the tongue and mucous membrane of the mouth, and a widespread purpuric eruption on the hands, feet, shoulders, neck, and face. He complained of a feeling of weakness, but was not distressed. His blood pressure was 170/110. Nothing abnormal was found in the cardiovascular, respiratory, nervous, and renal systems. The spleen was palpable, and enlarged lymph nodes were present in both axillae. There was typical spindling of the proximal interphalangeal joints of the fingers. Pain, swelling, and limitation of movement were also present in the wrists, elbows, ankles, and feet. At this time his haemoglobin was 90%, white blood cells 10,000 per c.mm. E.S.R. 46 mm. per hour, and platelets 163,000 per c.mm. Examination of a sternal marrow smear showed some hyaline degeneration of the megakaryocytes.

A transfusion of 2 pints (1,140 ml.) of whole blood was given and the bleeding stopped for three days. Epistaxis then recurred, and the patient complained of abdominal pain, nausea, headache, and diplopia. Haematuria developed and a subconjunctival haemorrhage appeared in the right eye. Ptosis became apparent and the power of accommodation was lost. Some weakness of the left leg was noted and the knee-jerk could not be elicited. There was no evidence of sensory loss. Paralysis of the third cranial nerve on the right side became complete. A further 2 pints of whole blood was transfused, but this did not control the bleeding. At this stage the platelet count had fallen to 20,000 per c.mm. The white-cell count was within the range of 5,600 to 8,200 per c.mm. The haemoglobin was 102%.

In view of the failure of transfusions to control bleeding, and the presence of a persistently low platelet count, dimercaprol was given in doses of 150 mg. six-hourly. After the second injection the patient complained of a feeling of constriction in the chest, with flushing. The individual dose was reduced to 100 mg. and no further reactions occurred. A total of 1.3 g. was given over six days. The bleeding diminished, and ceased during the course of treatment with dimercaprol. After withdrawal of the drug no further haemorrhage occurred. The platelet count remained low during dimercaprol treatment, values between 30,000 and 50,000 per c.mm. being recorded. A further transfusion of 1½ pints (850 ml.) of fresh whole blood was given without appreciable effect on the platelet count. Power in the left leg gradually improved, but the knee-jerk did not return for about eighteen months. Paralysis of the right third cranial nerve slowly improved and recovery was complete in seven months.

Comment.—Although the administration of dimercaprol coincided with the cessation of haemorrhage there was no appreciable rise in the platelet count for a further 25 days, and it is doubtful if dimercaprol, in the doses given, materially influenced the course of the disease. The most remarkable feature in this case was the localized lesions of the nervous system. Damage to the central nervous system can undoubtedly complicate the administration of gold. Mollard (1935) reported a case which developed bulbar palsy and paralysis of the right facial nerve. Hinault and Mollard (1934) described a patient in whom facial neuralgia, impairment of accommodation, and transitory blindness arose during the administration of gold. Sundelin (1941) collected 107 cases in which some evidence of neurological damage had occurred as a result of gold therapy. Hartfall *et al.* (1937), Cohen *et al.* (1947), and Doyle and Cannon (1950) reported cases of severe peripheral neuritis, in all of which recovery was eventually complete. In the present case it is difficult to be certain whether the neurological symptoms were due to the direct effect of the gold on the central nervous system or to small haemorrhages into the brain stem and cord. In view of the widespread purpura, the latter is considered to be the more likely explanation.

Case 2

This patient, a woman aged 44, was admitted to hospital with a history of profuse vaginal bleeding and widespread purpura for 12 days. She had suffered from rheumatoid arthritis of a very mild type for three years. Six months before admission her symptoms became much more acute and a course of gold was recommended. Injections were given at weekly intervals. A substantial clinical improvement was noted when a total of 0.85 g. had been given. After an interval of three weeks she received three further injections, each of 0.05 g. She noticed a metallic taste in her mouth and complained of general malaise. Menstruation began at the normal time, but bleeding became profuse and continuous. A generalized purpuric eruption appeared. She was admitted to another hospital and found to be severely anaemic. She received 4 pints (2,280 ml.) of blood before transfer to the rheumatic unit.

On admission her haemoglobin was 35%, red blood cells, 2,000,000 per c.mm.; white blood cells, 2,050 per c.mm.; and platelets, 20,100 per c.mm. The bleeding-time was raised to 20 minutes. Purpura and ecchymoses were present on the hands, thighs, and buttocks. Physical examination revealed only minimal evidence of rheumatoid arthritis in the small peripheral joints. The spleen was not palpable and no other abnormality was discovered. Vaginal haemorrhage continued. Her condition improved somewhat with repeated transfusions, 5 pints (2,840 ml.) of packed cells being given initially. The haemoglobin rose to 53% and the red cells to 3,270,000. In view of the value of A.C.T.H. and cortisone in idiopathic thrombocytopenic purpura (Bethell *et al.*, 1951; Wilson and Eisemann, 1952; Faloon *et al.*, 1952) and in other varieties of toxic reaction to drugs (Steinberg and Roodenburg, 1951), it was decided to explore their value in this condition. A total of 100 mg. of A.C.T.H. was given by the intravenous route, in the course of three days, combined with 40 mg. of "acthar gel" twice daily. Little evidence of haematological response appeared. The platelet count remained less than 40,000 per c.mm. and the bleeding-time remained over 10 minutes. The red-cell count and haemoglobin level fell from their post-transfusion levels to 2,780,000 per c.mm. and 47% respectively.

The dose of acthar gel was therefore increased to 60 mg. twice daily from the fourth day of treatment and, in addition, 100 mg. of cortisone was given daily by mouth. Apart

from a transitory fall in the bleeding-time, there was no evidence of any improvement. The dose of cortisone was increased to 125 mg. and subsequently to 150 mg. daily, while the dose of A.C.T.H. was reduced to 40 mg. daily. Signs of fluid retention appeared, in the form of ankle and sacral oedema, basal pulmonary crepitations, and a rise in systolic blood pressure. The bleeding-time remained over 10 minutes. Vaginal bleeding continued. The haemoglobin had fallen to 42%, red-cell count to 2,410,000, and platelets to 18,000 by the fourteenth day of treatment. The white-cell count was reduced to 2,500 per c.mm. A further 3 pints (1,700 ml.) of blood was given.

In view of the complete absence of any signs of improvement in the haematological condition, it was not considered justifiable to continue with cortisone or A.C.T.H. When the hormones were finally withdrawn, a total of 1.41 g. of A.C.T.H. and 1.75 g. of cortisone had been given. It would appear, therefore, that these hormones may be of little value in the treatment of severe cases of thrombocytopenic purpura following the administration of gold. It is of interest to note that the E.S.R. fell from initially high levels of 120 and 130 mm. in one hour to within normal limits during the period of hormone therapy and rose rapidly after withdrawal. The capillary resistance, measured by the method described by Robson and Duthie (1950), also rose during the period of hormonal treatment and fell after withdrawal. A similar effect on the blood pressure was noted. Eosinophils were absent from the peripheral blood during the period of hormonal therapy.

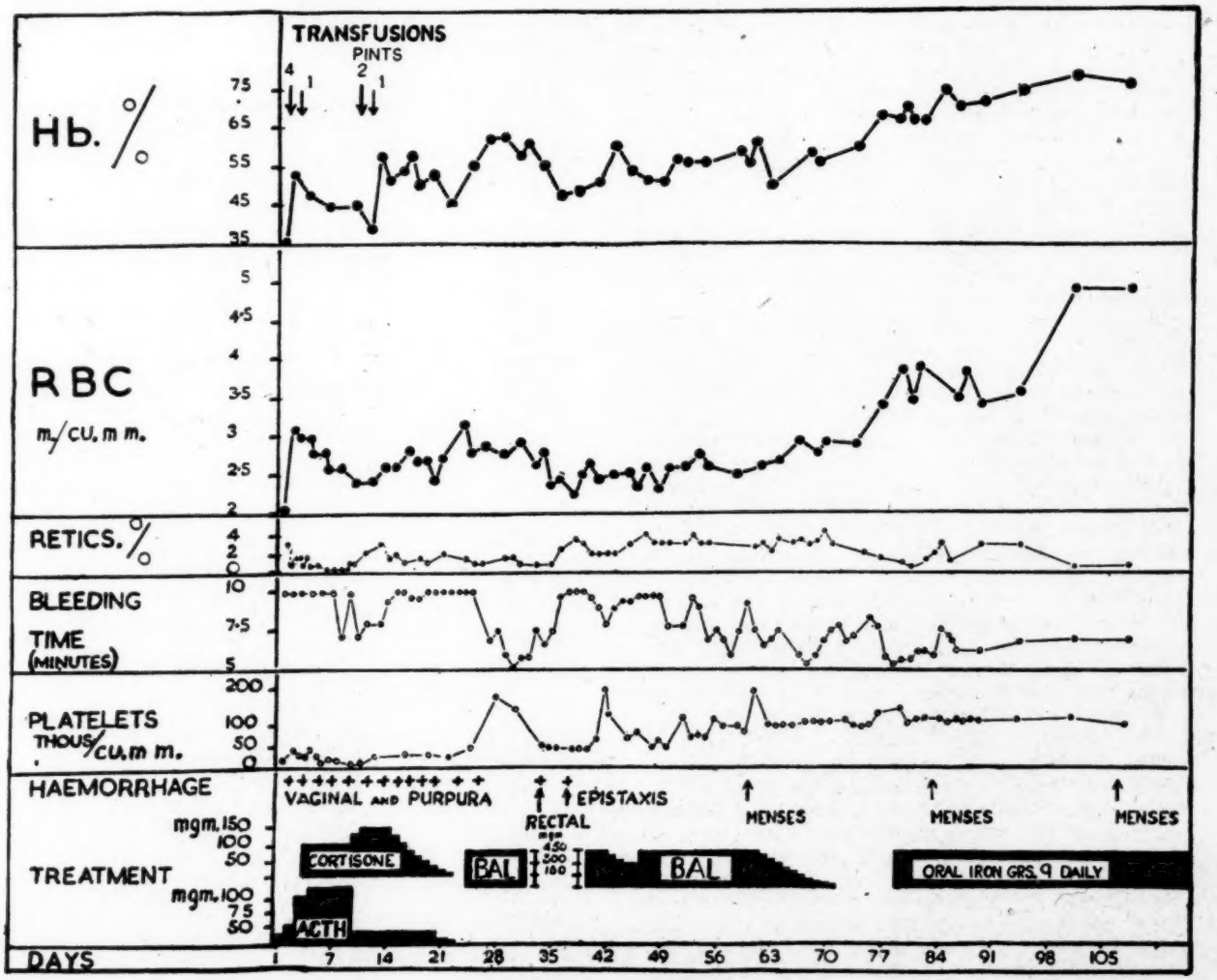
Dimercaprol was then given in doses of 150 mg. eight-hourly for 10 days. There was an immediate and dramatic response (see Chart). Haemorrhage ceased, the bleeding-time fell rapidly, while the platelet count rose from 20,000 to 200,000 per c.mm. and the haemoglobin level rose from 52% to 60%. On the abrupt withdrawal of dimercaprol this improvement was quickly reversed. The platelet count and haemoglobin level fell, the bleeding-time rose again, and there were further episodes of haemorrhage, this time from the rectum and nose.

After an interval of six days dimercaprol was again given in doses of 450 mg. daily and the haematological response was unequivocal (see Chart). Five days later the dose was reduced to 300 mg., but some deterioration again took place. The dose was restored to the former level of 450 mg. daily and continued for a further 12 days. During this time normal menstruation occurred, and it was thought to be safe to begin withdrawal of the drug. This was done during the course of 10 days, without any sign of relapse. The patient's condition improved rapidly and there has been no relapse for one year. A feature of interest that occurred during administration of the second course of dimercaprol was a marked eosinophilia. The eosinophil count rose abruptly to 1,200 per c.mm. from its previous level of 50. This marked eosinophilia persisted during the second course of dimercaprol and subsided slowly as the drug was withdrawn.

No flare-up in the joints occurred after the withdrawal of cortisone, A.C.T.H., or dimercaprol.

Discussion

Several points of interest emerge from a study of the response to treatment of these two patients. In Case 1 purpura and thrombocytopenia appeared after the administration of a relatively small amount of gold (0.22 g.).



Dimercaprol given in the recommended doses (total 1.2 g.) appeared to have little immediate effect on the course of the condition. The platelet count remained at a very low level for 25 days after its administration was stopped. The fact that the cessation of haemorrhage coincided fairly closely with the administration of dimercaprol may be of little significance, as bleeding was not a prominent feature and anaemia did not develop. The neurological complications in this patient have already been discussed.

In Case 2 1 g. of gold had been given before purpura appeared. Haemorrhage was severe and continuous. A marked degree of anaemia rapidly developed. Repeated transfusions were necessary as a life-saving measure, but were of very temporary benefit. Large doses of A.C.T.H. and cortisone had no significant effect on the platelet count or the anaemia. The bleeding-time did show some improvement, and the capillary resistance, as measured by the negative-pressure method (Robson and Duthie, 1950), rose sharply from an initially subnormal level. This is an observation of some interest, as it would suggest that the reduction in the strength of the capillary wall found in thrombocytopenia of both the idiopathic and the toxic type may be of little importance as a cause of haemorrhage. The findings in this patient would suggest that there is a closer interrelationship with the platelet count, but other as yet unknown factors must be concerned, as low counts are not infrequently found in the absence of bleeding (see Case 1). The failure of these hormones is in marked contrast to their effects in the idiopathic variety of thrombocytopenic purpura, in which a response occurs in most cases, although it may be incomplete and temporary.

Davidson *et al.* (1952) have also reported the failure of A.C.T.H. to influence the haematological condition in one case of thrombocytopenic purpura following the administration of gold. Virkkunen (1952), however, describes the effect of A.C.T.H. and cortisone in two cases with severe thrombocytopenic purpura after gold therapy. In one case a short course of cortisone produced a substantial rise in the platelet level, with an immediate fall on withdrawal. A subsequent more prolonged course produced a permanent return of the platelet level to normal. In the other case a total of 2 g. of A.C.T.H. was administered over one month, without any improvement in the extremely low platelet count. Clinically the patient improved without further haemorrhagic phenomena, but the thrombocytopenia persisted until four months after treatment, when a spontaneous remission occurred.

In Case 2 the response to dimercaprol was prompt and unequivocal. Cessation of treatment was followed by deterioration. Resumption of dimercaprol restored the position, but reduction of the daily dose to 300 mg. was again followed by relapse. The critical dose at this time lay between 300 and 450 mg. daily. The occurrence of normal menstruation was thought to indicate that dimercaprol might safely be withdrawn, and this proved to be the case. This patient received a total of 15.575 g. of the drug without any evidence of toxic effects. An interesting finding was the marked eosinophilia during the second course of dimercaprol. This is difficult to explain, as the patient had no clinical signs of hypersensitivity such as rash or fever. The presence of a persistent leucopenia would suggest a depression of all the cellular elements of the bone marrow. It may be that the adequate removal of the gold in the tissues by dimercaprol prevented further damage of the marrow and thereby avoided the possible onset of agranulocytosis or aplastic anaemia.

The pharmacological properties and therapeutic uses of dimercaprol have been reviewed by Weatherall (1948). Its action depends on its ability to form stable complexes with the heavy metals. By so doing it transfers the toxic element from the cells to the tissue fluids, from which it is excreted in the urine. In doses above 5 mg. per kg. body weight it may cause lacrimation, salivation, vomiting, and a rise in blood pressure, but permanent damage to organs has not been reported. It is not known why certain individuals develop toxic reactions to gold, but in such individuals it would appear necessary to protect any susceptible tissues from the damaging action of gold until it is no longer being absorbed from tissue depots in significant quantities. This point is well illustrated in Case 2. It would seem that in the past some of the poor results reported in the treatment of thrombocytopenic purpura with dimercaprol may have been due to failure to give the drug in large enough doses for long enough periods. Results are likely to be more satisfactory if dimercaprol is given immediately toxic effects appear, as in these circumstances it may be possible to clear gold both from the damaged tissues and from the tissue depots, thus protecting susceptible cells from further injury. In recent years the successful use of much higher doses has been reported. Montgomery (1950), in two cases of gold dermatitis, gave a total of 9.6 g. in one case and 11.9 g. to the other over periods of 12 and 8 weeks respectively. One patient developed skin sensitivity to dimercaprol, but suffered no other ill effects.

Summary

Two cases of thrombocytopenic purpura following gold administration are described.

Unusual neurological signs occurred in one case, probably due to small haemorrhages into the cord and brain stem.

One case appeared to show no response to dimercaprol, but it is now considered that the total dosage given was inadequate.

One case showed no response to large doses of A.C.T.H. and cortisone, but responded promptly to dimercaprol.

The need for a higher daily dose and more prolonged courses of dimercaprol are discussed.

During the period when these cases were studied, the Rheumatic Unit, Northern General Hospital, was in receipt of grants from the Medical Research Council and the Nuffield Foundation. The cortisone and A.C.T.H. were supplied by the Medical Research Council, to whom we are indebted.

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HYPOPARATHYROIDISM AND PSEUDO-HYPOPARATHYROIDISM

BY

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Hypoparathyroidism is well recognized as a complication of thyroidectomy. In most series of cases reported in the literature the incidence has been less than 1% after operations for hyperthyroidism, the figures ranging from 0.2% (Cattel, 1934) to 3.5% (Lachmann, 1941); in about half the cases the tetany is only transient. Idiopathic hypoparathyroidism is generally regarded as a rarity. Only 60 to 70 proved cases have been recorded in the literature, and only three of these have been reported from this country (Humphreys, 1939; Himsworth and Maizels, 1940; Jordan and Kelsall, 1951). Still rarer, perhaps, is the condition of pseudo-hypoparathyroidism, described by Albright *et al.* (1942), which results from abnormal resistance to parathyroid hormone rather than from deficient secretion. Only 18 cases have so far been reported.

We have been impressed by the variety of ways in which this group of disorders may present, and by the ease with which they may escape recognition. We believe that they may not be as rare as is commonly supposed. We therefore record three cases of idiopathic hypoparathyroidism, together with three illustrative cases of the post-operative condition and one case of pseudo-hypoparathyroidism. This last case has already been reported elsewhere (Bishop and de Mowbray, 1951), and is, so far as we are aware, the first to be recorded in this country.

Case 1. Idiopathic Hypoparathyroidism

This patient, a man aged 44, first noticed stiffness of his leg muscles after mild exercise when aged about 12. At 22 he began to develop progressive failure of vision, at 40 a cataract was removed from his left eye. At the age of 32 he began to have carpopedal spasms, and between the attacks he had difficulty in moving his joints, owing to a feeling of "hardness" in the muscles. A few years later he developed sudden involuntary "flinging" movements of his limbs, occasionally causing him to fall to the ground. For four years he had difficulty in initiating sudden leg movements, on account of spasm of the muscles. For about 20 years his wife had noticed a gradual loss of his critical and introspective faculties, and, more recently, he himself had been aware of an impairment of his powers of concentration and emotional control. He had never had an operation on the thyroid gland. He had been treated for some years as a hysteric and later as an epileptic (one of his sisters had suffered from epilepsy in the past).

On examination he was facile and emotionally unstable, and liable to attacks of uncontrolled and sometimes inappropriate laughter. His powers of concentration were limited and variable, and intelligence tests showed deterioration (Wechsler Bellevue, 61; progressive matrix, Grade V). Chvostek's and Trousseau's signs were positive. A mature cataract was present in his right eye, and one had already been removed from his left eye. His skin and nails were normal, but his teeth were poor in quality.

Investigations.—The serum calcium was 6.5 mg., the phosphate 4.3 mg., and the alkaline phosphatase 18 units per 100 ml. The Sulkowitch test showed no calcium in the urine. The Ellsworth–Howard test gave a normal response to parathyroid hormone (Fig. 1). The faeces contained no excess of fat. *X*-ray films (Figs. 2 and 3) showed radiating striae of calcification in the caudate nucleus areas of the brain and possibly calcification in the cerebellum. Two of the last molar teeth were unerupted (Fig. 2). The pelvic bones showed increased density, with some calcification of the tendon insertions. The electroencephalogram

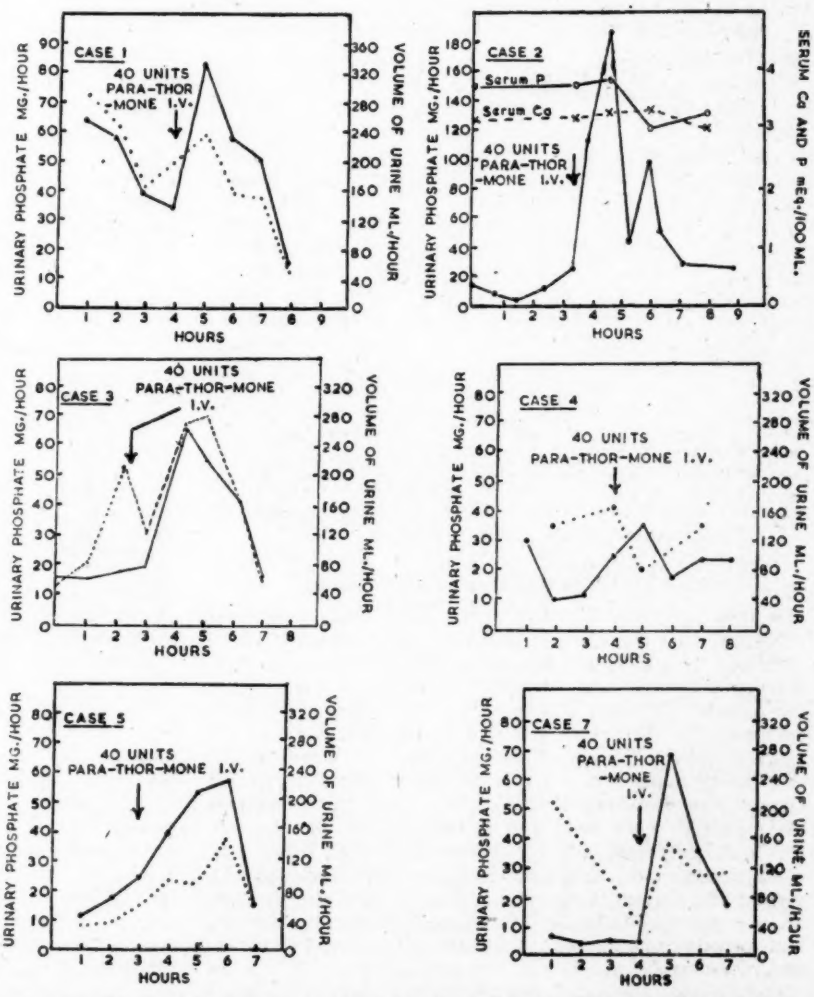

FIG. 1.—Ellsworth–Howard test. Administration of parathyroid hormone to subjects with true hypoparathyroidism (and to normal subjects) leads to a marked increase in urinary phosphate excretion and a water diuresis. There is no significant response in the case of pseudo-hypoparathyroidism. The patients were under basal conditions, except in Case 2. ——=Urinary phosphate level. .....=Urinary volume.

showed abnormally slow dominant frequency at 6 to 7 cycles a second in the post-central areas. These waves were bilaterally symmetrical, and were inhibited by visual attention; hyperventilation led to a slight increase in dominant frequency. The electrocardiogram showed low voltage in all leads, especially in the T waves, and the Q–T interval was prolonged.

FIG. 2.—Case 1. Idiopathic hypoparathyroidism. Bilateral calcification in the basal ganglia, arranged in radiating striations. One of the unerupted molars is also shown.

Treatment.—Dihydrotachysterol, 1 ml. (1.25 mg.), was given three times daily, and the dose was gradually reduced to a maintenance level of 1 ml. daily. Latent tenany was abolished after five days, and the stiffness of the limbs disappeared. His mental state, however, remained unchanged. The cataract was successfully removed from his right eye. The electroencephalogram improved, now showing a dominant alpha rhythm at 8 cycles a second, and the electrocardiogram returned to normal.

FIG. 3.—Outline drawing of radiating striae of calcification shown in Fig. 2.

Case 2. Idiopathic Hypoparathyroidism

A man aged 41 was seen by an ophthalmic surgeon in February, 1951, on account of failing vision of three years' duration. He was found to have extensive bilateral posterior lamellar cataracts, and a reducing substance was present in the urine. He was therefore referred for a physician's opinion. On further questioning it was revealed that 12 years previously the hair of his head had fallen out rapidly in a patchy manner, and that it had never completely grown again. The eyebrows had also fallen out, and several of his nails had been shed and had only partially regrown. He had never had any symptoms of tetany, except for some paraesthesiae in the hands and a tendency to paraesthesiae and cramps in the legs. His wife said that for two or three years he had been becoming more morose, irritable, and forgetful, and had been losing interest in his appearance and cleanliness. He had never had an operation on the thyroid gland, and there was no relevant family history.

On examination the vertex of the scalp was almost completely bald, and at the sides of the head were patches of thinning, where the hairs were small, white, and brittle. Several of his nails had only partially grown again and were ridged, broken, and brittle (Fig. 4): scrapings from them failed to show any fungus. Chvostek's sign was positive, but Trousseau's sign was negative. The blood pressure was 130/70 and the urine normal.

FIG. 4.—Case 2. Trophic changes in the finger-nails.

Investigations.—The serum calcium was 5.8 mg. and the phosphate 6.2 mg. per 100 ml. The Ellsworth–Howard test showed a normal response to parathyroid hormone (Fig. 1). *X*-ray films showed no calcification in the brain and the bone density was normal.

Treatment.—Dihydrotachysterol and calcium lactate were given, as shown in Fig. 5, the maintenance dose being 1 ml. and 75 gr. (5 g.) daily, respectively. The mental symptoms resolved soon after treatment was begun and the paraesthesiae disappeared. The nails have completely regrown (Fig. 6) and there is some evidence of regrowth of hair. There is no apparent change in his cataracts, and it has not so far been necessary to operate on them.

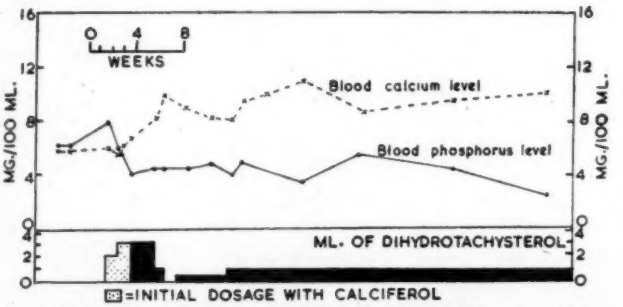

FIG. 5.—Case 2. Response of blood calcium and phosphate levels dihydrotachysterol dosage. (50,000 units of calciferol = 1 ml. of dihydrotachysterol.)

FIG. 6.—Finger-nails of Case 2 after six months' treatment with dihydrotachysterol.

Case 3. Idiopathic Hypoparathyroidism

This patient, a man aged 50, had been seized with severe cramps in the hands after an attack of "influenza" when aged 31. The cramps continued intermittently, being brought on particularly by his work as a boot-repairer. In March, 1933, two months after the onset of symptoms, he had an exceptionally severe attack, which involved the muscles of the face and throat, causing dyspnoea, and he was admitted to hospital. On admission Chvostek's and Trousseau's signs were strongly positive, and the serum calcium level was 5.4 mg. and the serum phosphate level 8 mg. per 100 ml. Within six hours after injections of calcium chloride and "para-thor-mone" the symptoms

disappeared. He was discharged from hospital, free of symptoms, with a serum calcium level of 8.1 mg. per 100 ml. and taking calcium gluconate, 2 dr. (8 g.) thrice daily, and "ostelin," 3 minims (0.18 ml.) thrice daily, and 2 pints (1.1 litres) of milk daily. On return to work, however, he continued to have cramps. These became more severe again and he was readmitted to hospital in December, 1933. At that time *x*-ray films showed normal bone density and there was no excess of fats in the faeces. He was treated with para-thor-mone 10 units weekly. Eight years after the onset of the tetany his vision began to fail. A cataract was removed from the left eye seven years later (in 1949), and another was removed from the right eye in December, 1951.

When first seen by us, on February 14, 1952, he was still having intermittent attacks of tetany, mainly after any infection or anxiety, or during the winter and spring. The spasms were painful and were accompanied by sweating. He had never had any epileptiform convulsions. He was not receiving any regular treatment, but was given injections of para-thor-mone during attacks of tetany, with complete relief. He had never had an operation on the thyroid gland.

On examination Chvostek's and Trousseau's signs were positive. There were no trophic changes in the skin, hair, or nails. The blood pressure was 130/80 and the urine normal.

Investigations.—The serum calcium was 6 mg. and the serum phosphate 4 mg. per 100 ml. He had, however, received an injection of para-thor-mone a fortnight previously, and after a further 10 days without treatment the calcium fell to 5.5 mg. and the phosphate rose to 5.4 mg. per 100 ml. The serum alkaline phosphatase was 7.5 units per 100 ml. The Ellsworth–Howard test gave a normal response to parathyroid hormone (Fig. 1). *X*-ray films showed normal bone density and no evidence of calcification in the brain.

Treatment.—The serum calcium level has been raised to 8.8 mg. per 100 ml. by treatment with dihydrotachysterol, and the serum phosphate figure is now 3.6 mg. per 100 ml.

Case 4. Pseudohypoparathyroidism

This patient, a girl aged 18, developed tetany after operation for an acute mastoid infection at the age of 6. The symptoms were alleviated by "ostocalcium," but she continued to have mild tetany from time to time and the serum calcium level remained below normal. She had always been undersized and mentally retarded. The menarche was at the age of 13, since when she had menstruated normally. There was no relevant family history.

On examination she was dwarfed, thick-set, and somewhat obese. Her height was 55 in. (140 cm.), span 53½ in. (136 cm.), floor to pubis measurement 26½ in. (67 cm.), and pubis to vertex 28½ in. (72 cm.). Thus the limbs were a little short in comparison with the trunk. The hands and fingers were short and there was a characteristic roundness of the face (Fig. 7). *X*-ray films showed disproportionate shortening of the fourth and fifth metacarpals. The tibiae were slightly bowed, especially the left one. Secondary sexual development was normal, except for a slight degree of hirsutism. There were no defects in the skin, hair, and nails, and no lens opacities, but the teeth were poorly formed. Chvostek's and Trousseau's signs were positive. The blood pressure was 110/65 and the urine normal.

Investigations.—The serum calcium was 6 mg., phosphate 6.8 mg., and alkaline phosphatase 2.7 units per 100 ml. The Sulkowitch test showed no calcium in the urine and quantitative estimation showed only 12 mg. per 24 hours. The Ellsworth–Howard test showed almost complete resistance to parathyroid hormone (Fig. 1). *X*-ray films showed patches of calcification in the basal ganglia of the brain. The bone density was normal. Epiphysial closure was well advanced for her age. Small patches of calcification were seen in the soft tissues of the limbs, some of them being deposited along the course of the blood vessels. The first premolars of the lower jaw and the first molars of both jaws were unerupted and none of the second molars showed proper root formation. Renal function was impaired; the urine could be diluted to 1002 and concentrated to 1020, but the maximal urea concentration was only 1.08%. Intravenous pyelography was normal.

FIG. 7.—Case 4. Pseudo-hypoparathyroidism. Rounding of the face.

Treatment.—Dihydrotachysterol, 1 ml. (1.25 mg.), was given three times daily. Calcium was detectable in the urine after one week, and within three weeks the serum calcium level had risen to 11.6 mg. per 100 ml. The symptoms and signs of tetany disappeared, and the patient has remained well, with normal serum calcium and phosphate levels, on a maintenance dose of 0.5 ml. of dihydrotachysterol daily.

Case 5. Post-operative Hypoparathyroidism

A woman aged 37 had had two operations for hyperthyroidism at the ages of 31 and 35. On the second occasion a total thyroidectomy was performed, as the surgeon was suspicious that the goitre might be malignant. After operation she lost her voice, and in the course of five months became myxoedematous. She responded to treatment with thyroid, but then began to have epileptiform convulsions with asphyxial symptoms. She developed a marked laryngeal stridor, due to abductor paralysis of both vocal cords, presumably from injury to the recurrent laryngeal nerves. A tracheotomy was performed, but this failed to relieve the asphyxial attacks. The epileptiform convulsions were not relieved by phenytoin sodium, 1½ gr. (0.1 g.) twice daily, and one year after the second operation she also began to have paraesthesiae in the neck and in the right arm and leg. At this time, while her blood pressure was being recorded, it was noticed that she showed a positive Trousseau's sign, and the serum calcium level was found to be 7.2 mg. (phosphate 4.2 mg.) per 100 ml.

Calcium lactate, 75 gr. (5 g.) and calciferol, 6,000 units daily, failed to alter the serum calcium level, and after a week she was given 9 ml. (11.25 mg.) of dihydrotachysterol daily. The serum calcium level rose to 10 mg. per 100 ml. after nine days and the fits ceased to occur. For the past four years she has been maintained on a dose of 6,000 units of calciferol daily, together with 75 gr. (5 g.) of calcium lactate. It has not been possible to dispense with the tracheotomy, and it is therefore clear that the laryngeal palsy was not a result of the hypocalcaemia. It is of interest that both she and her siblings had convulsions in infancy, which suggests that her threshold for convulsions is low.

Case 6. Post-operative Hypoparathyroidism

A married woman aged 46 underwent three operations for a non-toxic goitre between the ages of 15 and 17. She apparently had no symptoms until five years later, when she began to have generalized convulsions. These were thought to be epileptic and were treated as such for a number of years. Some 14 years later it was recognized that she was suffering from chronic tetany. At that time she showed bilateral cataracts, and the serum calcium level was 6.5 mg. per 100 ml.; the serum phosphate level was

not estimated. She was treated with a high calcium intake, hydrochloric acid, and ammonium chloride, with only partial relief. Two years later she was given calciferol, 100,000 units daily, with remarkable improvement. The cataract in the right eye was removed at the age of 44. A year later she began to develop menopausal symptoms, accompanied by emotional instability and a tendency to overbreathe, thus precipitating further symptoms of tetany.

When first seen by us she had been taking vitamin D, 100,000 units daily, for eight years, but was still having tetany. Chvostek's sign was weakly positive, and Trousseau's sign was strongly positive, being accompanied by emotional disturbance and overbreathing. The hair of her head was generally sparse. The blood pressure was 170/110 and the urine normal. The serum calcium was 7.1 mg., phosphate 4.5 mg., and alkaline phosphatase 9.5 units per 100 ml. The electrocardiogram showed left axis deviation with low voltage T_1, inverted T_2 and T_3, and depression of the ST segment. The Q–T interval was prolonged. *X*-ray films showed marked calcification in the basal ganglia and in the region of the cerebellum. The bone density was normal. The Ellsworth–Howard test showed a poor response to the injection of 40 units of para-thor-mone (Fig. 1).

Dihydrotachysterol was substituted for calciferol, and the symptoms and the serum calcium level were controlled by a maintenance dose of 0.66 to 1 ml. daily. Three months later the cataract in the left eye was successfully removed, but a month later still, after a respiratory infection, the symptoms of tetany and epilepsy relapsed to their original state. Neither the symptoms nor the serum calcium level could be controlled by as much as 4 ml. of dihydrotachysterol daily, and treatment with calciferol was resumed instead. The symptoms were well controlled by a dose of 200,000 units daily, and four successive normal serum calcium figures were obtained within a fortnight under in-patient conditions. Five days after discharge from the ward she developed anorexia, followed by thirst, polyuria, an unpleasant taste in the mouth, weakness of the limbs, dyspnoea, and vomiting, and she was readmitted five days later in a confused state, with muscular atony and a serum calcium level of 15.9 mg. per 100 ml. The calciferol was discontinued, but she became maniacal and deluded, and had to be transferred to a mental ward. She subsequently developed a hemiparesis, and the blood urea rose to 72 mg. per 100 ml. Both the mental symptoms and the hemiparesis cleared up within 10 days, and the serum calcium level fell to normal after a further four weeks.

Case 7. Post-operative Hypoparathyroidism

A married woman aged 23 underwent thyroidectomy for hyperthyroidism at the age of 21. Four days after operation she developed tetany, which was relieved by injections of calcium gluconate and dihydrotachysterol. Treatment with dihydrotachysterol was continued only intermittently, in view of difficulty in obtaining supplies. Fifteen months later she became pregnant, and continued to term in spite of the fact that she received no calcium or dihydrotachysterol during pregnancy. There was, however, a return of the attacks of tetany during labour. Lactation was terminated after two months on account of a breast abscess. When inadequately treated she was inclined to emotional instability and hyperventilation, with exacerbation of her tetany. She was investigated when not under the influence of treatment, and showed positive Chvostek's and Trousseau's signs, a serum calcium level of 6.1 mg. and a phosphate level of 4.9 mg. per 100 ml., and only a trace of calcium in the urine. The Ellsworth–Howard test showed a normal response to parathyroid hormone (Fig. 1). There were no defects in the skin, hair, or nails, and no opacities in the lenses on examination with a slit-lamp.

Her symptoms were controlled, and a normal serum calcium level was maintained, on a dose of 1 ml. of dihydrotachysterol daily.

Mode of Presentation

Tetany.—Three of our cases presented with this symptom (Cases 3, 4, and 7). Carpopedal spasms also occurred in Cases 1, 5, and 6, but they were overshadowed by other manifestations. In Case 2 the only symptoms of tetany which could be elicited were mild paraesthesiae and cramps. The symptoms may indeed vary from trivial paraesthesiae to severe generalized spasms. Sometimes these involve the respiratory muscles, and, rarely, the diaphragm is affected, with fatal results. Shelling (1935) describes other occasional manifestations of tetany, such as strabismus, nystagmus, abnormalities of the pupils, dysphagia, dysarthria, symptoms of pyloric or intestinal obstruction, bronchial spasm, retention or incontinence of urine, peripheral oedema, Raynaud's phenomenon, tachycardia, cardiac irregularities, or even sudden cardiac arrest. Boothby *et al.* (1931) describe weakness and fatigability of the muscles, and Lachmann (1941) describes intermittent pareses in the limbs in one case. Infantile convulsions may occasionally be due to hypoparathyroidism, which may be physiological in the neonatal period or may represent the onset of idiopathic hypoparathyroidism (Bakwin, 1939).

Epilepsy.—Cases 5 and 6 presented with typical major seizures, and were treated for some time as cases of idiopathic epilepsy. In Case 6 the fits did not begin until five years after thyroidectomy, which made the diagnosis more elusive. Approximately 40% of the cases of idiopathic hypoparathyroidism recorded in the literature have presented with epilepsy, and many cases have escaped recognition as a result of this. Either major or minor seizures may occur. They are not necessarily associated with frank symptoms of tetany, and, when they are, their onset is often independent, but they usually cease when the serum calcium level is restored to normal. The electroencephalogram may show typical epileptic changes, and the abnormal waves tend to disappear with correction of the serum calcium level, but the record does not necessarily become normal, suggesting either that these patients are latent epileptics or that irreversible cerebral changes have occurred (Kowallis, 1941; Taubenhaus and Engle, 1945; Mortell, 1946; Gotta and Odoriz, 1948). In Case 1 there were no true epileptic manifestations, but there was a history of seizures of a myoclonic pattern.

Ectodermal Lesions.—Case 2 showed patchy loss of hair, loss of the eyebrows and eyelashes, and deformity of the nails. More commonly, the hair of the head is generally sparse, and rarely there is complete alopecia. There may also be loss of pubic and axillary hair. In some cases the skin becomes dry, rough, and scaly. The nails and the mouth may become infected with moniliasis in idiopathic hypoparathyroidism (Thorpe and Handley, 1929; Sevringhaus, 1942; Sutphin *et al.*, 1943; Talbot *et al.*, 1943). Impetigo herpetiformis has also been described as an association with chronic tetany (Lachmann, 1941).

Cataracts.—Case 2 attended an eye hospital with cataracts in the first instance and was referred to a physician only because of the finding of a trace of reducing substance in the urine. Cataracts were also present in Cases 1, 3, and 6, and had to be extracted. They may occur in chronic hypocalcaemia from any cause (Albright and Reifenstein, 1948). Although some authors have claimed that those occurring in hypoparathyroidism have a distinct pattern and that they tend to develop in the subcapsular layer, O'Brien (1932) came to the conclusion that there was no characteristic morphology. Cataracts may develop in the absence of frank symptoms of tetany or when the symptoms have become much milder, either with or without treatment. They may develop rapidly, leading to blindness within a few months (Emerson *et al.*, 1941).

It is clear that cases of hypoparathyroidism may present in various ways and that they may be referred in the first instance to various special departments. Thus Case 1 first came to a neurological clinic, and Case 2 to an eye hospital, and it is likely that other cases might be found in skin clinics. Though classical carpopedal spasms may easily be

recognized, mild tetany may be mistaken for acroparaesthesiae, "neuritis," "fibrositis," "cramps," or "hysteria." More cases of hypoparathyroidism might come to light if the diagnosis were borne in mind in such cases, and in cases of epilepsy, in cases of cataract occurring in young persons, and in patients with trophic lesions in the skin, hair, and nails.

Other Manifestations

Changes in Teeth.—When parathyroid deficiency arises in childhood the enamel is often deficient and shows transverse ridges, and changes occur in the dentine. Sometimes there may be delay or failure of eruption. These changes do not occur when the disease arises in adult life, and decalcification never occurs (Albright and Strock, 1933).

Mental Changes.—Anxiety symptoms were prominent in Cases 6 and 7, and there was a resulting tendency to hyperventilation, precipitating further attacks of tetany. Case 1 showed intellectual deterioration and emotional instability and incongruity, and Case 2 showed moroseness, irritability, impairment of memory, and loss of interest in his appearance. Frank psychoses of manic-depressive and delusional types have been described (Barr *et al.*, 1938; Eaton and Haines, 1939; Greene and Swanson, 1941; Scarlett and Houghtling, 1944). These mental changes usually resolve within a few weeks after the serum calcium is restored to normal, which suggests that they are the direct result of hypocalcaemia. Mental retardation has also been recorded in a number of cases of idiopathic hypoparathyroidism arising in childhood.

Papilloedema occurs occasionally. It subsides when the serum calcium level is restored to normal (Albrecht, 1923; Shelling and Goodman, 1934; Barr *et al.*, 1938; Hurxthal, 1942; Sutphin *et al.*, 1943; Mortell, 1946; Berezin and Stein, 1948). The combination of papilloedema and epilepsy may suggest a cerebral tumour.

Physical Development.—In a number of cases arising in childhood the patients have been undersized. The height has been recorded in the literature in 10 cases in which the patient has reached the age of 18. The heights ranged from 57 to 67 in. (145 to 170 cm.), average 61¼ in. (156 cm.). In some cases puberty has been delayed and secondary sexual characters have been underdeveloped.

Other Endocrine Disorders.—These are seldom found. Hypothyroidism occasionally occurs in post-operative cases (as in Case 4); it has also been described in two idiopathic cases (Himsworth and Maizels, 1940; Lachmann, 1941). Addison's disease has been associated with idiopathic hypoparathyroidism in three cases (Sutphin *et al.*, 1943; Talbot *et al.*, 1943; Leonard, 1946). In Leonard's case necropsy showed atrophy of the adrenal glands as well as absence of the parathyroids; in the case of Sutphin *et al.* there was tuberculous infection.

Hypoparathyroidism has not been recorded in panhypopituitarism, and there is no good evidence that a pituitary parathyrotrophic factor exists. This subject is reviewed by Collip (1940), Törnblom (1949), and Engfeldt (1950).

Diagnosis

Blood Chemistry.—The serum calcium figure is reduced and the serum inorganic phosphorus level is raised. The normal range for the serum phosphate level is given by Albright and Reifenstein (1948) as 3.2 mg. per 100 ml. ± 0.5 but in our laboratories it is from 2.5 to 5 mg. per 100 ml. Drake, Albright, *et al.* (1939) regard a raised serum phosphate level as an essential diagnostic criterion. This distinguishes hypoparathyroidism from other low-calcium disorders, such as rickets, osteomalacia, and steatorrhoea, in which the blood is unsaturated with calcium and phosphorus and both levels tend to be low. The only other condition in which a low serum calcium level and a high serum phosphorus level are found is chronic renal disease; this should therefore be excluded. In Case 1 the serum phosphorus level was never higher than 4.5 mg. per 100 ml.; this figure is raised by Albright and Reifenstein's standards, though it falls within our normal range.

Radiological Findings.—Calcification was present in the basal ganglia in three of our cases (Cases 1, 4, and 6). In Cases 4 and 6 it was punctate, but in Case 1 it was arranged in radiating striations (see Fig. 2). The radiological aspects of Cases 1 and 3 have already been reported (Medill, 1951), and the subject is reviewed by Camp (1947), Siglin, Eaton, Camp, and Haines (1947), and Foley (1951). The bone density is normal or increased. It was increased in Case 1, but was normal in the others. Rarefaction does not occur as a primary feature of hypoparathyroidism; it was reported in one of Emerson, Walsh, and Howard's cases (1941) and in one of Lachmann's cases (1941), but in both of these it was probably due to post-menopausal osteoporosis. The metabolic and radiological changes can best be explained on the basis of the theory of Albright and his colleagues that the primary action of parathyroid hormone is to increase the excretion of phosphorus in the urine, leading to a fall in the serum phosphate level and a compensatory rise in the serum calcium level. It follows that in hypoparathyroidism the initial change will be a rise in the serum phosphate level, followed by a compensatory fall in the serum calcium level. Since the blood is fully saturated with calcium phosphate, a rise in the phosphate concentration, together with continued absorption from the intestine, will lead to a tendency to supersaturation of the blood, with an increase in deposition of bone salt and an increase in bone density (Albright and Reifenstein, 1948). The cerebral calcification may be due to the same mechanism, but it is not clear why the brain is affected and other soft tissues are not.

Electrocardiographic Changes.—The characteristic change of hypocalcaemia is seen—namely, prolongation of the Q–T interval.

Electroencephalographic Changes.—There may be: (*a*) slow waves of 2 to 5 cycles a second (as in Case 1), usually in series of three or four waves, but sometimes in stretches of up to 10 seconds; (*b*) typical epileptic changes, with groups of slow waves and spikes; (*c*) a continuous generalized disturbance of rhythm; or (*d*) a normal record (Gotta and Odoriz, 1948).

Pseudo-hypoparathyroidism

This consists of three independent genetic defects. (1) There is a disturbance of the peripheral action of parathyroid hormone, producing effects exactly similar to those of true hypoparathyroidism, except that the injection of parathyroid hormone usually fails to increase the excretion of phosphate in the urine (see Fig. 1). The parathyroid glands are shown to be normal or hyperplastic on biopsy. (2) There is a dyschondroplasia, resulting in a short stature and in shortening of various bones, particularly the metacarpals and metatarsals. (3) There is a tendency for the subcutaneous tissues to become calcified and to form bone. The appearance of these patients is characteristic. They are short and thick-set; the face is rounded (see Fig. 6) and they are often mentally retarded. All these features are well shown by Case 4. The suggestion that the condition is due to a genetic disturbance is confirmed by its occurrence on two occasions in a pair of twins, and in another case in a mother and child (Elrick *et al.*, 1950).

The distinction from true hypoparathyroidism is to a large extent academic, as the treatment is the same, but it is of considerable general interest, since it shows that an endocrine disorder may result not only from failure of secretion of a hormone but also from an abnormal peripheral response to it.

Treatment

Para-thor-mone is of very limited value, since acute cases following operation are more rapidly controlled by administration of calcium salts, and in chronic cases the hormone has four disadvantages: (1) it is expensive, (2) it has to be given by injection, (3) it is apt to give rise to local

reactions, and (4) it leads to antibody-formation and therefore begins to lose its effect after a few weeks (Albright and Ellsworth, 1929).

Either calciferol (vitamin D_2) or dihydrotachysterol should be used. These substances differ in chemical structure only in the saturation of a double bond. Whereas parathyroid hormone increases the excretion of phosphate in the urine but has no effect upon calcium absorption, calciferol acts principally upon calcium absorption, and only to a less extent upon phosphate excretion. Dihydrotachysterol, on the other hand, more closely resembles parathyroid hormone in its action, in that it acts primarily upon excretion of phosphate and only to a less extent upon absorption of calcium (Albright *et al.*, 1938). There is also evidence that both calciferol and dihydrotachysterol have a direct action upon bone, leading to resorption and mobilization of calcium (Selye, 1932).

Dihydrotachysterol is usually given in doses of 3 ml. (3.75 mg.) daily initially, the dose being reduced to 0.5 or 1 ml. (0.625 to 1.25 mg.) daily for maintenance treatment. Calciferol usually has to be given in doses of 100,000 to 400,000 units daily (Sevringhaus and St. John, 1943) or occasionally 500,000 units (Himsworth and Maizels, 1940).

McLean (1941) states that the toxic effects of vitamin D have been overemphasized, and that many of the effects reported by earlier workers were due to the high toxisterol content of the original preparations. The dangers are by no means negligible, however, as Anning *et al.* (1948) and Howard and Meyer (1948) have pointed out. Anning *et al.* found toxic symptoms in 19% of 200 patients who were receiving 100,000 to 150,000 units of calciferol daily for treatment of various skin dieases. Howard and Meyer describe toxic effects in 11 cases but only one of these was suffering from hypoparathyroidism. The symptoms of intoxication consist of thirst, anorexia, vomiting, tiredness, malaise, nausea, headache, constipation, abdominal pain, polyuria, intolerance of noise, loss of weight, excitability, photophobia, rhinorrhoea, generalized pruritus, and, occasionally, drowsiness and coma, psychic disturbances, impaired memory, paraesthesiae, muscular pains and atony, and amblyopia. Howard and Meyer report calcium deposits beneath the conjunctival basement membranes, as seen with the slit-lamp, in 9 of 11 cases, and albuminuria in seven cases. All their cases showed impairment of renal function, with blood non-protein-nitrogen levels of 46 to 106 mg. per 100 ml. Psychotic changes as severe as those occurring in Case 6 do not appear to have been reported previously. It seems that the risk of toxic effects is smaller in cases of hypoparathyroidism, and in fact few such cases have been reported. But Howard and Meyer's case and our Case 6 show that the risk exists and that the consequences may be serious.

It is probable that toxic symptoms are due to an individual idiosyncrasy or to impaired renal function. In Case 6 they resulted from a dose of 200,000 units daily, and in Howard and Meyer's case of hypoparathyroidism on a dose of 300,000 units daily, whereas many other patients have received much higher doses without untoward effects. Both in Case 6 and in Howard and Meyer's case the symptoms occurred within three weeks of starting calciferol treatment, though our Case 6 had previously received a prolonged course of 100,000 units daily, and had been thought to have developed mild intoxication some years previously.

If toxic symptoms appear the drug must be discontinued immediately, fluids must be given copiously, and the calcium intake must be reduced to a minimum. Howard and Meyer found that the serum calcium level remained raised for two to four months, and in one case for as long as 20 months, during which time the blood urea level remained slightly raised and renal function remained impaired. Under such conditions there is, of course, a risk of widespread soft-tissue calcification. In our Case 5 the serum calcium level returned to normal within four weeks.

Similar toxic effects have been observed by some workers with dihydrotachysterol, but these have not been of serious import; no fatal case has been reported so far as we are aware, and no evidence has been obtained of chronic damage, even when the serum calcium level has been raised temporarily as high as 15 mg. per 100 ml. (McLean, 1941). Dihydrotachysterol is probably less likely to give rise to hypercalcaemia than is calciferol, since it does not predominantly influence calcium absorption.

Summarizing, dihydrotachysterol is preferable to calciferol on theoretical grounds, in that it more closely resembles parathyroid hormone in its action. In practice there seems to be little difference between them so far as their effect upon the clinical and biochemical picture is concerned. But, assuming that an average maintenance dose of dihydrotachysterol is 0.5 ml. daily, and that this is equivalent to 100,000 units of calciferol daily, the expense of treatment amounts to approximately £1 a month in the case of dihydrotachysterol, as against approximately 1s. a month in the case of calciferol. On the other hand, calciferol is probably more likely to produce hypercalcaemia, since it acts primarily upon calcium absorption. Occasional cases show resistance to dihydrotachysterol (Holtz, 1933), and cases of pseudo-hypoparathyroidism may be relatively resistant to dihydrotachysterol as well as to parathyroid hormone (Albright *et al.*, 1942).

We have not found it necessary to give calcium salts as well, and, as dosage has to be readjusted repeatedly, it would appear to be easier to deal with only one variable than with two. Nor have we paid any attention to the diet, as no patient is likely to maintain a strict intake of calcium and phosphorus, and it does not seem to be necessary to control it. Milk should, however, not be taken in excess, for its phosphorus content is high (Albright and Reifenstein, 1948).

Albright and Reifenstein state that treatment can be controlled adequately by testing the urine for calcium, with Sulkowitch reagent. We have not found the Sulkowitch test to be reliable in practice. In Case 6 only a moderate reaction was obtained, even though the patient was in a state of acute hypercalcaemia, and on other occasions we have found subnormal calcium levels when the Sulkowitch reaction was optimal. Sevringhaus and St. John (1943) and Jordan and Kelsall (1951) have also found the test to be not completely reliable. In our experience, it is necessary to control treatment by means of repeated estimations of the serum calcium level. The chief value of the Sulkowitch test is that it can be performed regularly by the patient himself, and that a strongly positive or negative reaction should warn him that his treatment requires immediate readjustment. It is important that the test-tubes should be cleaned with distilled water, as tap-water usually contains considerable amounts of calcium.

Dosage may have to be increased during pregnancy, but a few cases improve at this time, as in Case 7 and in Scarlett and Houghtling's case (1944), and some cases quoted by Lachmann (1941). The dose may also have to be increased during periods of physical and mental strain, during infections, and after operations.

In practice we have found that stabilization is not nearly as easy as might appear at first sight, and that the dosage repeatedly needs to be adjusted. The principles of treatment are in fact very similar to those involved in the treatment of diabetes mellitus.

The aim should be not only to control symptoms but to maintain a persistently normal level of serum calcium, in the attempt to avoid such serious complications as cataracts, mental changes, and calcification in the brain.

Summary

Three cases of idiopathic hypoparathyroidism, three post-operative cases, and one case of pseudo-hypoparathyroidism are described.

The cases usually present with tetany, the symptoms of which are very variable. Epilepsy is also a common presenting symptom. Some cases may present with

cataracts or with ectodermal defects. Other manifestations include defects in the teeth, psychoneurotic or psychotic disturbances, papilloedema, and physical and mental retardation.

The serum calcium level is reduced and the serum phosphate level is raised.

X-ray films often show calcification in the brain, especially in the basal ganglia, and normal or increased density of the bones.

The electrocardiogram shows a prolonged Q–T interval and the electroencephalogram shows abnormal slow waves or epileptic changes.

Pseudo-hypoparathyroidism is due to abnormal resistance to parathyroid hormone and presents exactly similar features, together with a dyschondroplasia, resulting in a short stature and shortening of the metacarpal and metatarsal bones, and a tendency to metaplastic bone formation in the soft tissues.

Treatment is by means of dihydrotachysterol or calciferol. Theoretically, the former is preferable, in so far as it more closely resembles parathyroid hormone in its action; but in practice there is little to choose between them. Dihydrotachysterol has the disadvantage that it is considerably more expensive, while calciferol is probably more apt to give rise to hypercalcaemia.

Though idiopathic hypoparathyroidism and pseudo-hypoparathyroidism are generally regarded as rare disorders, it is likely that more cases would come to light if the diagnosis were borne in mind in cases with obscure paraesthesiae and pains and cramps in the limbs, and in cases of epilepsy, of cataract in young persons, and of defects in the ectodermal tissues.

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Addendum.—Since this article was submitted for publication we have found it necessary to increase the doses of dihydrotachysterol (A.T.10) considerably above the amounts indicated in the text. Thus Case 4 now requires 6 ml. daily, and Case 7 4 ml. daily, of the material at present available in this country, in order to maintain a normal serum calcium level. Case 3 has required 3 ml. throughout. We are in close consultation with the manufacturers, who are investigating this discrepancy.

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THE RECENT TRENDS OF INFECTIOUS DISEASES IN CHILDHOOD

BY

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Since the inception of the National Health Service Act in 1948 the level of the notifications of three common infectious diseases of childhood—scarlet fever, whooping-cough, and measles—has been above that of the immediately preceding years. During the first quarter of 1951 the weekly notifications of both measles and whooping-cough reached the highest point since these diseases were made notifiable, and an even larger incidence of measles has been recorded in the first quarter of 1953. Diphtheria, on the other hand, has declined consistently and rapidly, and the average weekly notifications during the first quarter of 1953 were only 20, compared with 900 for the first quarters of 1940 and 1941. The number of notifications and the deaths per 1,000 notifications for these four diseases, for the years 1940 to 1952, are shown in Table I. The incidence of measles, scarlet fever, and whooping-cough rose in 1948, and it may well be thought that the recent high level of these diseases is due only to the operation of the National Health Service, because medical advice is more often sought regarding mild cases. It is to be noted, however, that the incidence of all three was unusually large for the first six months of 1949—that is, preceding the operation of the Service—as can be seen from Figs. 1, 2, and 3.

Table I shows that the fall in the fatality rates, which had been apparent since 1942, was accentuated in 1948 for measles and whooping-cough. The fatality rates for these diseases were about half of those in the preceding year. The obvious explanation for the large drop in fatality is that more mild cases were being notified. Scarlet fever did not show a large fall in the fatality rate, and the decrease was no larger than would have

TABLE I.—*Infectious Diseases: Notifications and Death Rates. England and Wales*

Year	No. of Notifications				Deaths per 1,000 Notifications			
	Measles	Whooping-cough	Scarlet Fever	Diphtheria	Measles	Whooping-cough	Scarlet Fever	Diphtheria
1940	407,468	53,545	63,778	45,445	2·1	12·7	2·4	54
1941	407,949	173,249	58,051	49,432	2·8	13·8	2·3	53
1942	285,446	65,986	83,830	40,042	1·6	12·1	1·2	45
1943	373,788	96,105	113,917	33,277	2·1	11·6	1·1	41
1944	157,125	93,944	90,581	22,085	1·5	11·2	1·2	40
1945	445,412	62,663	72,174	17,580	1·6	11·0	1·1	39
1946	159,553	92,892	56,099	11,601	1·3	8·7	0·7	39
1947	393,116	92,657	57,246	5,492	1·6	9·8	0·7	44
1948	399,185	146,372	73,940	3,531	0·8	5·1	0·5	44
1949	385,753	102,801	70,186	1,874	0·8	5·1	0·4	45
1950	367,598	157,752	65,878	959	0·6	2·5	0·5	51
1951	616,093	169,347	48,735	658	0·5	2·7	0·8	50
1952	389,505	114,868	67,251	375	0·4	1·6	0·3	85

been expected from a continuation of the existing trend. It would appear that clinically recognizable attacks of scarlet fever were fairly completely notified prior to 1948. The trend of diphtheria appears to be unaffected by the events of 1948, although the fall in the number of notifications was not proportionately so large as in the preceding year. The percentage rates of decline for 1945 to 1948 were 21, 33, 53, and 36 respectively. The case fatality of diphtheria in 1948 was the same as in 1947. There is no evidence, therefore, from the notifications or deaths that the trend of diphtheria was disturbed in 1948.

It seems of interest to examine the trends of whooping-cough, scarlet fever, and measles in an attempt to decide whether more complete reporting can wholly or partially explain their increase in incidence or whether there has been a real increase in prevalence.

Scarlet Fever

The number of notifications of scarlet fever has been generally accepted as a good index of the actual incidence for the 20 years prior to 1948. On the basis of notifications it has been estimated that about 10% of the child population suffered from a notifiable attack of scarlet fever before the age of 15. This value was in close agreement with the proportion found in field surveys—for example, Stocks's (1930) investigation in St. Pancras. The records of over 10,000 children in 26 English public boarding schools examined during 1930–4 (Epidemics in Schools, 1938) showed that a history of an attack of scarlet fever before entry into school was given by 8.3% of the boys and 7.2% of the girls.

It follows that it was not to be expected that the operation of the National Health Act would materially affect the reported incidence of scarlet fever, since there was no evidence that any appreciable number of cases escaped notification. The rhythm of the seasonal trend was altered just before the operation of the Health Service, when instead of the expected fall in incidence in the first quarter of 1948 the number of notifications slightly exceeded those in the preceding fourth quarter (Fig. 1). This phenomenon of the postponement of the seasonal peak to the first quarter occurred again in 1951–2. The difference between the expected and the actual number of notifications is so large that it seems extremely unlikely that the exceptional trend in the first quarter of 1948 can be explained by the inclusion of mild cases which in preceding years would have escaped notification. The deaths per 1,000 notifications given in Table I also show that no large abrupt change occurred in 1948. It would appear, therefore, that there was a real increase in the prevalence of scarlet fever just before the introduction of the Health Service.

The age of attack of scarlet fever differs from that of measles or whooping-cough. The school-child has a greater rate of attack from scarlet fever than the pre-school child, while the reverse is the case for the other two diseases. The attack rate for recent years is shown in Table II. There is a suggestion that the attack rate for the pre-school child compared with that of the school-child has become relatively larger in the last four years of the period. This may have been due to young children receiving medical attention who prior to 1948 would not have been seen and notified by a medical practitioner. Just as likely an explanation is that there has been a real shift in the age of attack.

TABLE II.—*Notifications of Scarlet Fever per* 100,000 *Living. England and Wales*

Year	Ages 0–4	Ages 5–14	Ratio (5–14/0–4)
1944	652	1,056	1·62
1945	531	836	1·57
1946	410	647	1·58
1947	362	658	1·82
1948	538	839	1·56
1949	580	770	1·33
1950	565	679	1·20
1951	403	504	1·25
1952	522	724	1·38

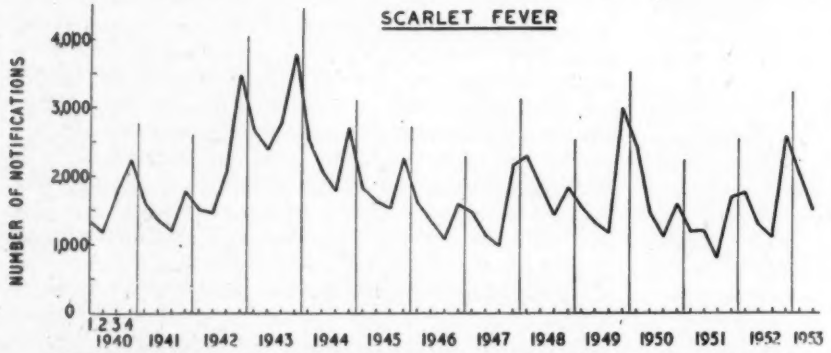

FIG. 1.—Number of notifications of scarlet fever by quarters, England and Wales.

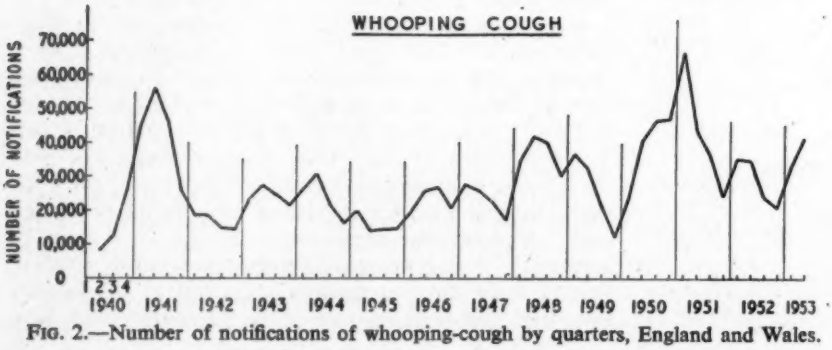

FIG. 2.—Number of notifications of whooping-cough by quarters, England and Wales.

Whooping-cough

The numbers of notifications of whooping-cough prior to 1948 were known to be defective, and from them the estimated proportion of children who had an attack of whooping-cough before the age of 15 was 15%. This value was much below that of about 70% found in field surveys or in the inquiry into the 26 English public schools (Epidemics in Schools, 1938), when 70% of the boys and 67% of the girls had a history of whooping-cough before entry. The available evidence leads to the conclusion that only about one-quarter of the children with whooping-cough were notified in the years immediately preceding 1948. Probably in many

cases medical attention was not sought. In discussing this deficit, Stocks (1949) stated : "Whether or not the National Health Service, coupled with the increased notification fee for whooping-cough, will result in an increase in the proportion of children and adults notified remains to be seen, but there is room for a large increase."

A large rise in incidence began before the start of the Health Service in 1948, and the number of notifications in that year was larger than in any of the six preceding years—though less than in 1941 (Fig. 2). A further large rise occurred in 1950–1, when the outbreak lasted two years. Table I shows that the recorded fatality rate, which had been falling slowly since 1941, fell abruptly in 1948 to almost half the level of 1947. The large outbreak in 1950–1 was accompanied by a further halving of the recorded fatality rate. The trend of this rate suggests that since 1948 the increase in the numbers of notifications of whooping-cough is due to more cases coming to the notice of the medical practitioners than formerly.

If the evidence of the field inquiries is accepted that 60 to 70% of the child population suffer an attack of whooping-cough before the age of 15, then even the higher incidence of whooping-cough since 1948 would imply that less than half of the cases of whooping-cough were notified during 1948–52. It seems, therefore, that most of the increase in the number of notifications in the past five years could be accounted for by increased case-finding, but the rather erratic decline in the recorded fatality rate makes an estimation of the amount of real increase in prevalence rather uncertain. This uncertainty is increased by immunization against whooping-cough, which has been practised during this period. If immunity has been conferred on any appreciable proportion of the child population then a part of the increase in the number of notifications was due to an increased prevalence of the disease.

Whooping-cough is a disease of the pre-school child, and the attack rate for children aged 0 to 4 is slightly more than three times that of children aged 5 to 14. The ratio of the attack rate of the pre-school children to that of the schoolchildren has been practically constant during recent years.

Measles

The estimated proportion of children notified as suffering from measles between 1940, when measles was first made notifiable, and 1947 was slightly less than 50%. This compares with 72.5% for boys and 63.1% for girls with a history of measles before entry into English public schools in 1930–4 (Epidemics in Schools, 1938). Many children suffering from a mild attack of measles were not seen by a medical practitioner, and Stocks (1949) estimated that the notification rate represented only about two-thirds of the true incidence. He stated: "The National Health Services and raising of the notification fee in 1948 may result in some increase in the proportion who are notified." Prior to 1948 measles had a well-marked biennial distribution with alternating years of high and low incidence (Fig. 3). In years of low incidence the maximum occurred in the second quarter, while in years of high incidence the peak was in the first quarter, except for 1945, when the number of notifications in the second quarter slightly exceeded the number in the first.

According to this pattern 1948 should have been a year of low incidence, but in fact the number of notifications slightly exceeded those in 1947. The outbreak in 1948, with a large rise in the second quarter, differed from preceding major outbreaks in seasonal distribution. The distinctive peak in the alternate first quarters reappeared in 1949, 1951, and 1953, but the incidence in the inter-epidemic years did not fall to the low level recorded prior to 1948, and the notifications in 1950 and 1952 were twice the number recorded in 1944 and 1946. A large fall in the fatality rate supports the hypothesis that many more mild cases than usual were notified. The fatality rate had been falling since 1941, with a large fall in the years of low incidence and a small rise in the years of high incidence. From the trend of the fatality rates a value of 1.1 instead of 0.8 would have been expected in 1948.

If we assume that the difference between the observed and the expected fatality rate was due to an increase in case-finding then the number of notifications necessary for 326 deaths to give a rate of 1.1 per 1,000 would be 296,000, and the difference between this value and the actual notifications gives 100,000 as the estimated increase due to better case-finding and reporting. Reducing the number of notifications in 1948 by 100,000 still leaves a total which is almost twice that of 1946 or 1944, the preceding non-epidemic years. On this basis it appears that the increase in incidence in 1948 was contributed in equal parts by a real increase in prevalence and by more complete notification, and the disease was almost twice as prevalent in 1948 as in 1946 or 1944.

It was expected that the operation of the National Health Service would appreciably raise the number of persons seeking medical attention and the number of consultations, especially among the previously non-insured section of the population, mainly women and children, in the lower-income groups. How far this group contributed to the increase in the number of notifications of infectious diseases is a matter of speculation. A comparison between the experience of different types of areas selected according to their degree of industrialization presents some difficulties.

TABLE III.—*Number of Notifications of Measles*

Year	Group 1	Group 2	Ratio
1947	4,081	2,588	1·6
1948	7,264	4,893	1·5
1949	7,101	4,134	1·7
1950	5,551	2,473	2·2
1951	11,671	7,966	1·5
1952	7,203	4,543	1·6

The two chief are: (*a*) the dispersal of the child population during the war years, which invalidates any comparison before 1946, and (*b*) the only information at present available regarding occupations and industries is that of the 1931 census. Despite these difficulties, it was thought it would be of interest to compare two contrasting groups of London boroughs. These groups were chosen on the basis of the social classes of the occupied males.

Group 1 consisted of six boroughs—Hampstead, Holborn, Kensington, Lewisham, Wandsworth, Westminster—with the largest proportion of occupied males in social classes I and II and a low proportion in classes IV and V. Group 2 comprised six boroughs—Bermondsey, Bethnal Green, Finsbury, Poplar, Shoreditch, Southwark—which had the largest proportions of the male population in social classes IV and V. Although the classification of these boroughs depends

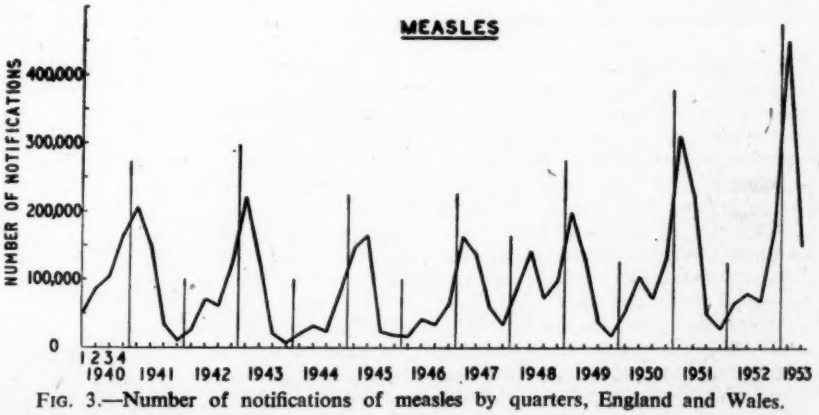

FIG. 3.—Number of notifications of measles by quarters, England and Wales.

on outdated material it is not likely that any borough has moved from one extreme to the other in social grading. The trend of the incidence of measles in both these groups of boroughs was very similar, and there was no difference of any importance between them. A summary of their positions is given in Table III. It appears from these values that the relative incidence of measles was constant during the period, although Group 1 had relatively a larger outbreak than Group 2 in 1950 owing to a summer rise in incidence. The introduction of the National Health Service in 1948 did not have any differential effect on the incidence.

In recent years the measles attack rate has been twice as large among pre-school children as among school-children, and the ratio of these attack rates has been practically constant during the past nine years.

Summary

The number of notifications of scarlet fever, whooping-cough, and measles rose in the six months preceding the operation of the National Health Service in 1948 and has remained above the level prevailing in 1946–7.

Scarlet Fever.—Although the incidence in the first quarter of 1948 was unusually high the subsequent level of the notifications does not suggest that the prevalence of scarlet fever has undergone much change in recent years. There is, however, a suggestion that since 1948 the disease has tended to be more concentrated on the pre-school child.

Whooping-cough.—A large increase in the numbers of notifications has occurred since 1948. If the pre-war estimate that 70% of the child population have an attack of whooping-cough before age 15 is still valid, then only about one-half of the cases are being notified. But if immunization against whooping-cough has been carried out on large enough numbers it is possible that the higher level of notifications since 1948 is due to a real increase in prevalence.

Measles.—The level of notifications of measles has increased in recent years. The whole of the rise in 1948 cannot be explained by increased case-finding and reporting, and it seems that there was a real rise in prevalence just before the operation of the National Health Service. The proportion of children under 15 who suffer a notifiable attack of measles has risen from about one-half in the early 1940's to about two-thirds in the last five years. It seems probable that there has been a real increase in prevalence during these years.

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The Pakistan Minister for Health, Dr. A. M. Malik, in his country's parliament last month, gave details of steps taken in co-operation with the World Health Organization to improve public health and provide facilities for medical treatment. He said that the United Nations International Children's Emergency Fund had offered a 700 tons annual capacity plant for making Pakistan self-sufficient in her requirements of D.D.T. Work on the construction of the buildings and installations of the plant at Naushera in the Frontier Province had progressed considerably, and the plant should go into production in July. A B.C.G. vaccination campaign had been started in 1949, and so far more than 2,200,000 persons had been vaccinated. In East Pakistan a three-year programme for improving teaching and practice facilities at a nursing school in Dacca had been launched.

CLINICAL AND CHEMICAL STUDIES IN HUMAN LACTATION*

VI. THE FUNCTIONAL CAPACITY OF THE BREAST

BY

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There is little published evidence about the relationship of the size of the breast to its functional efficiency, but it is generally held by clinicians that no strong relationship exists. On the other hand, there is a well-recognized relationship between the size and function of the cow's udder: Gowen and Tobey (1927) computed that 1 lb. (450 g.) of udder would produce 1 lb. (450 ml.) of milk in three hours. It is reasonable to expect that, if there were any clear relationship in women, then this knowledge would have been incorporated into the general folklore of lactation; but the only idea occurring sporadically in the old literature, and still commonly held to-day, is that the very large breast is likely to have a poor performance. Nevertheless, Lussky (1951), in a hospital study, found that successful lactation occurred in 50.2%, 36.6%, and 19.0% of women with "large," "medium," and "small" breasts respectively.

The capacity of the breast to secrete milk probably depends on the amount of functional tissue it contains, and this is not necessarily related to the size of the breast: not only is there a layer of subcutaneous fat of variable thickness, but the gland itself, as has been demonstrated in post-mortem material by Engel (1941), shows an enormous variation in the ratio of parenchyma to fibrous tissue, ranging from almost 100% secretory tissue to almost none.

It would nevertheless be surprising if there were no relationship whatever between the size of the breast and its functional ability, and it is of some clinical interest to determine accurately what that relationship is.

For comparative studies, an estimate of the amount of functional tissue might be made in the living subject by measuring changes in breast size occurring in response to the menstrual cycle or to pregnancy. Engel (1947) believes that subjective impressions of breast enlargement during the premenstruum are a good index of the breast's functional equipment, presumably on the basis that the enlargement is due to proliferation of glandular tissue. This may be so, but breast changes during the cycle are due only partly to such proliferation, and, in any case, mostly to non-secretory tissue; much of the enlargement may be caused by oedema in the stroma (Geschickter, 1945), perhaps as part of a more general mechanism of water retention, and not directly related to the amount of gland present. The enlargement which occurs in pregnancy is likely to be a more reliable index of the amount of functional tissue, since it is due mostly to the proliferation of the gland. No study of these changes has been reported.

Previous Technique of Breast Measurement

Ingleby (1949) measured wax impressions taken from serial plaster casts of the breasts of 17 women during the menstrual cycle, and appeared able to measure differences of the order of 30 ml. Geschickter (1945) estimated the menstrual enlargements of the breasts in two women by measuring the

*Parts I, II, and III were published in the *Journal* on January 23, p. 175; and Parts IV and V on January 30, p. 249.

differences in the amount of water required to fill a glass vessel, applied to the chest and enclosing the breast. He describes a difference in one subject of only 15 ml., but this difference is likely to be less than the experimental error of such a method. Reimann and Seabold (1933), incidental to a study of breast lesions during the menstrual cycle, calculated areas of the *x*-ray shadows of breasts in profile, but this method is clearly subject to a good deal of inaccuracy and is, in any case, not comparable with three-dimensional estimations.

The fundamental difficulty in the determination of breast volume by any method *in vivo* is to define the posterior surface; that is, the chest wall underlying the breast. If a plaster cast of the breast is taken, then it is not difficult to curve the posterior wall to an arbitrary approximation of the chest contour, but, if a series from the same subject are to be made, then an artificial "chest wall" must be made first and all subsequent models fitted to it, so that the posterior surface, if not true to life, is at least constant for all the models. The method of making plaster casts takes time and requires a considerable degree of co-operation from the subject. It is also unsatisfactory for the large pendulous breast.

Several indirect methods which might be used to assess the functional tissue of the breast have been suggested. Pickles (1953) has described two rather complex techniques which will indicate the amount of blood flow through the breast, but there is no evidence of a fixed relationship between blood flow and breast function, and there are many circumstances which will confuse such estimations. An even less direct method of estimating blood flow is by infra-red photography (Bowes, 1950), but the amount of incident light is difficult to control and quantitative interpretation of the photographs would not be simple.

Method

In this investigation a method of water displacement has been used to study breast size.

The apparatus is illustrated in Fig. 1. It consists of a "perspex" container,* shaped to fit closely to the average

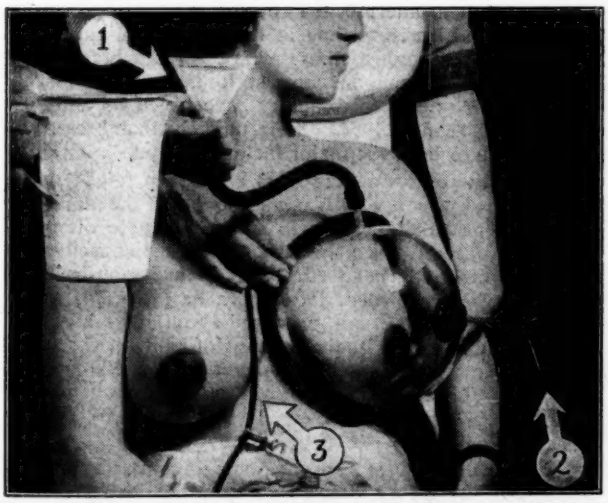

FIG. 1.—The method of estimating breast size. 1, Tube for filling apparatus. 2, Tube for emptying apparatus. 3, Tube for inflating the sealing ring.

chest wall round the breast, the seal being ensured by an inflatable rubber ring at the periphery. This ring is inflated by mouth and forms a cushion with a section of about ¼ in. (6 mm.) diameter. This arrangement proved to be leak-proof in all but two cases examined, the exceptions being small women with thin narrow chests.

With the subject seated upright, the apparatus is held firmly against the chest and filled with water at body temperature through an opening at the highest point, air escaping from a small hole alongside. When it is completely filled the water is drained off through another tube into a measuring cylinder. This volume of water is subtracted from the volume of the container, which has been previously determined using a perspex sheet curved to represent an approximately average chest wall. All measurements were made by one observer to ensure, so far as possible, that the rubber ring was inflated to a similar pressure for each observation, and that the apparatus was held against the chest wall with similar force. Results were reproducible to within 20–30 ml., an error of about 5%. Only the left breast was measured in all subjects except one, in whom the breasts were obviously asymmetrical, and in this woman both breasts were measured and the mean was taken.

Measurements were made on the seventh post-partum day, immediately following complete emptying by the "humalactor," in 86 primiparae and 23 multiparae. In nine of the primiparae and two of the multiparae measurements were also made during the course of pregnancy, beginning at the third month.

A detailed history of breast reactions during the menstrual cycle was obtained from 50 of the subjects whose breasts were measured.

The method of collection of milk samples has been previously described (Hytten, 1954a); the volume and composition of the seventh-day milk for all these subjects is included in Table II of an earlier paper of this series (Hytten, 1954c).

Results

For the 86 primiparae, the mean size of the empty breast on the seventh day of lactation was 787.0±219.6 ml., and for the 23 multiparae 756.9±314.0. The difference is not statistically significant.

Fig. 2 shows the relationship between breast size and the milk output on the seventh day of lactation. The calculated

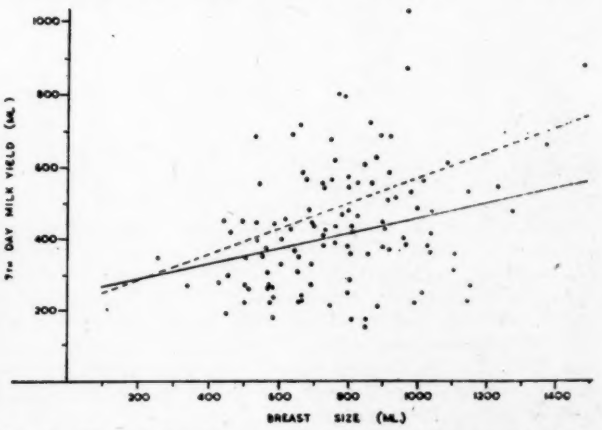

FIG. 2.—The relationship of milk yield on the seventh post-partum day to the size of the left breast. The regression lines calculated from these data are superimposed, the continuous line representing primiparae, the broken line multiparae.

regression lines for the primiparae and multiparae are superimposed. There was a correlation in the primiparous series ($r=+0.31$) significant at the 1% level, and a correlation of about the same magnitude for the multiparae ($r=+0.35$), although this was not statistically significant, probably because of the small numbers. The precision with which the seventh-day milk output could be predicted from breast size was not significantly different in the two groups, although this again may be due to the small sample.*

There was no correlation between the size of the breast and the fat, protein, or lactose content of the seventh-day milk.

*The apparatus may be obtained from Arnoplast Ltd., South Hillingdon Farm, Kelhead Avenue, Glasgow, S.W.2.

*The regression equation combining both sets of data is: Seventh-day milk output = 0.23 (breast size in ml.) + 260 ml. ±0.07.

In an attempt to reduce the effect of "fatness" on the size of the breast, an index was calculated by dividing the measured breast size by the weight-to-height ratio of the subject. In this way a breast of the same actual size would have a higher index in a thin woman than in a fat woman. The correlation between this index and the seventh-day milk output was no better than the correlation of the measured breast size and the seventh-day milk output.

Of the 50 women questioned about breast symptoms in the premenstrual period, only 10 (20%) had noticed any reaction at all. The mean seventh-day milk output of these 10 women was 573 ml., and for the remaining 40, 430 ml., the difference being statistically significant ($P<0.01$). The difference between the mean breast sizes of these two groups (838 ml. and 746 ml.) was also statistically significant ($P<0.01$).

The serial breast measurements taken throughout pregnancy on 11 subjects do not permit an accurate interpretation of the pattern of breast enlargement, since in this pilot experiment measurements were made during routine antenatal visits and were too widely spaced. Moreover, the estimation of small increases with an apparatus liable to an error of 20–30 ml. is not close enough. Nevertheless, in five cases there was almost no further increase after about the twenty-fourth week of pregnancy, the remainder continuing to enlarge, but at a slower rate than during the first half of pregnancy.

The Table shows the breast sizes at the third month of pregnancy, together with the post-partum breast sizes, milk output on the seventh post-partum day, and the ages of the 11 subjects.

Serial Breast Measurements in 11 Subjects

Case No.	Age	Left Breast Volume (ml.)			Seventh-day Milk Volume (ml.)
		3rd Month	Post-partum	Enlargement	
113	19	295	775	480	800
129	25	295	490	195	455
183	28	860	960	100	390
184	24	620	740	120	565
210	22	700	1,030	330	480
237	20	510	720	210	385
239*	31	410	760	350	805
246	25	990	1,050	60	250
248	21	785	1,050	265	565
263†	41	1,800	1,920	120	600
265	22	600	580	−20	180

* Second pregnancy. † Fifth pregnancy.

Results from the nine primiparae only were subjected to statistical analysis. There was a high correlation between the pregnancy enlargement of the breast and its milk output on the seventh post-partum day ($r=+0.87$), significant at 1%, and this can be clearly seen in the scatter diagram (Fig. 3). The regression line for primiparae has been drawn, and data for the two multiparae are also shown. There was no relationship between the initial size of the breast and its subsequent enlargement.

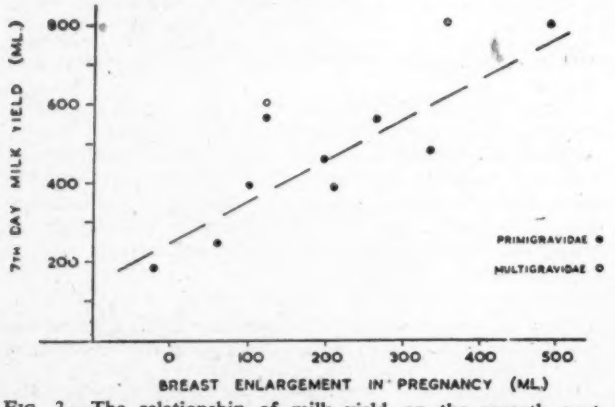

FIG. 3.—The relationship of milk yield on the seventh post-partum day to the enlargement of the breast which occurred during pregnancy.

There are clearly not enough results to test statistically the effect of age, but it can be seen from the Table that, apart from subject No. 265, who showed no enlargement at all, the four subjects aged 22 or under all had an enlargement of more than 200 ml., and the four older than this all enlarged by less than 200 ml. This confirms the clinical impression that while the very young primiparae are usually first seen at the antenatal clinic with tender swollen breasts and uncomfortably tight clothes, the older primiparae tend to show little reaction at the same stage of pregnancy.

Multiparae present an entirely different picture, since the glandular enlargement occurs into the loose stroma which has been left by involution from the previous lactation. There is therefore no tension, and the enlargement which occurs is not readily appreciated by either patient or examiner.

Discussion

Although there is an undoubted correlation between the size of the lactating breast and its milk production in hospital, the scatter is wide and the predictive value for an individual breast is obviously low. Fig. 2 does suggest, however, that the smallest breasts have a ceiling of performance on the seventh day.

In view of the differences in the actual shape of the chest wall which must occur between subjects, the results of measurement of breast size are not strictly comparable, but the error involved is probably slight in relation to the large range of values for breast size. Again, the milk output on any given day is not necessarily equivalent to the breast's potential yield, since it may have a considerable reserve which it does not exhibit in the absence of an appropriate demand. An artificial demand, such as the stripping of breasts by manual expression, may or may not provide this, although Waller (1950) claimed that the breast could be brought to maximum productivity during the first week of lactation by this means. However, Sydow (1952) has shown a close correlation between the milk output on the sixth day and the subsequent success of lactation, so that milk output in hospital can be accepted as of at least some value in indicating the true capacity of the breast.

It is difficult to interpret the striking relationship between breast size and breast-feeding in Lussky's series, since only half of the best group, those with "large" breasts, left hospital breast-feeding, in contrast to the overall hospital breast-feeding rate in this country of between 80 and 90% (Ministry of Health, 1951). It is unlikely that breast size was the only or even the major factor involved.

Two aspects of breast size must be kept in mind: one is the ability to produce milk, and the other the ability to store it. The small breast will suffer a double disability, and below a certain size this lack of storage capacity may become critical. Such an effect has been demonstrated in a previous paper (Hytten, 1954b). Subject No. 74, with a breast size of only 530 ml., produced about 120 ml. of milk at each feeding; that is, the amount of milk in the breast at, say, 2 p.m., after four hours' secretion, was 120 ml., and at 6 a.m., after eight hours' secretion, the amount was no more, clearly indicating an upper limit to storage capacity.

The range of breast capacity may, in part, explain the gradual falling off in breast-feeding which occurs during the course of the first two months, since lactation will become unsatisfactory when an infant has outgrown the supply which the breast can secrete or store.

The degree of breast enlargement occurring during pregnancy, which is probably due to changes in the functional tissues alone, would be expected to show a high correlation with lactation performance, although it must be stressed again that the results from so few subjects can only be tentative. Data for increase in size are of comparative value only, and in no sense absolute measurements of the gland itself; much of the increase must be due to other changes, such as increased vascularity, but these are likely to parallel closely the growth of the glandular tissue.

The measurement of the enlargement of the breast during the whole course of pregnancy is in practice extremely difficult, since women are not usually seen until the third month, by which time some enlargement of the breast has already occurred; in fact, it is usually claimed that the most rapid enlargement occurs during the first three or four months. The amount of enlargement which is missed, however, should be proportional to the total breast enlargement, provided that the measurements are made at approximately the same stage of pregnancy, so that for a comparative study it is probably no serious disadvantage to have missed the first two months. A large-scale investigation of measurements during the entire pregnancy will be required to establish the precise pattern of enlargement. The suggestion that the most rapid enlargement occurs at the beginning of pregnancy is probably fallacious, since it is based on subjective impressions of discomfort which are greatest at this stage, probably because of vascular engorgement. The unreliability of such subjective impressions as an index of enlargement is supported by the finding that there is seldom any difference in size between the breast on the seventh post-partum day and the same breast at the end of pregnancy, although it is also claimed that the first few days of the puerperium are a period of rapid enlargement.

For the same reason a history of change of size of clothes required during the pregnancy can be misleading. Subject No. 113, for example, whose left breast increased in volume by 480 ml. (160%) said she noticed almost no change in the size of the breasts and had worn the same brassière throughout pregnancy.

It has been suggested that a simpler investigation could be undertaken by serial circumferential chest measurements, but these are unlikely to provide anything but the crudest information, because the breast may change in shape without becoming any more protuberant. In fact, Engel's (1941) finding that breasts with little glandular tissue have it disposed round the periphery suggests that a "spreading out" rather than a forward enlargement may be commonly found.

The few cases so far investigated suggest that breast enlargement during pregnancy in primigravidae is greatly influenced by age, and additional evidence, to be given in a later paper, shows that failure to establish lactation owing to an inadequate milk supply increases rapidly with age in primiparae. It is possible that the long delay, sometimes of over twenty years, from the time of puberty may lead to disuse atrophy, or it may be that small breasts are among a number of physical characteristics which make early marriage and child-bearing less likely.

Although the reason for breast symptoms during the menstrual cycle is not altogether clear, their occurrence seems to be a rough indication that the breast is well equipped, although the converse is by no means necessarily true. The small proportion of women who report the phenomenon (20%) is perhaps surprising, but it agrees well with Engel's (1947) findings that only in 20–30% of breasts is the structure predominantly glandular.

The different reaction to pregnancy shown by multiparae may be due to their having already laid down much of their glandular tissue during a previous pregnancy. The primipara reacts by encroaching on and replacing the fatty stroma of the breast with growing gland, but when the lactation is over only a small part of this stroma is reformed (Geschickter, 1945), and the characteristic flabby breast, which again becomes firm only during another lactation, results. Although only two multiparae had their breasts measured during pregnancy in this series, it can be seen from Fig. 3 that they have a higher milk production for the same degree of enlargement in pregnancy than primigravidae. Similarly, although the difference between the correlations of breast size with milk output in primiparae and multiparae is not statistically significant, nevertheless the regression lines (Fig. 2) confirm this parity difference, the multiparae having a better milk yield for the same size of breast. This is in accord with the histological findings of Langer (1851), who found an increased amount of active breast tissue in women who had had repeated pregnancies.

Much of the variation in breast size and quantity of glandular tissue between individual women can probably be explained on the same basis as the difference in milk composition (Hytten, 1954d)—that is, the absence of selective breeding for lactational ability in human society. In other mammals the lactating gland is "characterized by the absolute predominance of glandular tissue" (Engel, 1947), but this is true of only 20–30% of human lactating breasts.

No relationship has been found between the size of a breast and the composition of the milk it secretes. It is probable, then, that women who are unable to provide milk of adequate composition are not necessarily the same persons who are unable to provide sufficient milk because of inadequate mammary glands. There are therefore two groups whose lactation will be unsatisfactory, and it is not surprising that so many mothers resort to artificial feeding because of a dissatisfied baby.

Summary

The size of the lactating breast was measured, after emptying in 86 primiparae and 23 multiparae, by a method of water displacement.

There was a significant correlation between breast size and the output of milk on the seventh day of lactation, but not with any of the major constituents of milk.

In nine of the primiparae and two of the multiparae the amount of breast enlargement during pregnancy was also measured; the first measurement was made during the third month of pregnancy. Wide variations in the amount of enlargement occurred, and this was closely related to milk output.

I am grateful to Professor Dugald Baird and to the staffs of the Midwifery Department and the Aberdeen Maternity Hospital for invaluable help; to Dr. I. Leitch, of the Commonwealth Bureau of Animal Nutrition, Bucksburn, for criticism and advice; to Dr. F. H. C. Marriott and Mr. I. MacDonald for statistical assistance; and to Mr. T. C. G. McKay, of the Aberdeen Royal Infirmary, for technical assistance with the apparatus.

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Because full particulars are not always given on prescriptions, the dispensing and pricing of prescriptions ordering certain Schedule IV poisons are proving unnecessarily difficult. This is stated in a recent notice from executive councils to practitioners (ECN/140). The difficulty particularly arises with drugs which are put up in several strengths, as unless the strength is stated prompt dispensing becomes impossible. Common examples of such drugs are "amytal" tablets (amylobarbitone), "amytal sodium" capsules (amylobarbitone sodium), "anthisan" tablets (mepyramine maleate), "benadryl" capsules (diphenylhydramine hydrochloride), "butazolidin" tablets (phenylbutazone), "nembutal" capsules (pentobarbitone sodium), "phenergan" tablets (promethazine hydrochloride), phenobarbitone tablets, "seconal sodium" capsules (quinalbarbitone sodium), quinalbarbitone tablets, and various sulphonamide preparations. In addition to the name, quantity, and dose of these drugs, the strength must also be given.

SPONTANEOUS REGRESSION OF THE GLANDS IN HODGKIN'S DISEASE

BY

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In view of the recent emphasis on the treatment of Hodgkin's disease, it is timely to remember that the enlarged glands may regress spontaneously. The purpose of this paper is to report three cases (Cases 1–3) in which this occurred and to refer to others collected from a survey of the hospital records.

In the first patient the regression was so striking and the restoration to apparently normal health so remarkable that the diagnosis was doubted even though supported by a gland biopsy. Only after a recurrence was it accepted. Shortly afterwards the second patient was admitted with a similar story. Meanwhile the diagnosis in the third patient had passed through a similar cycle to that of the first.

A review of the records of the Royal Victoria Infirmary from 1948 to 1952, inclusive, revealed 29 acceptable cases in which to study the occurrence of this phenomenon. All underwent biopsy or necropsy. Five showed it clearly and six less definitely.

Case Reports

Case 1.—A farmer aged 46 attended first on October 2, 1952. One month previously he had developed glands in his neck associated with sweating bouts and persistent itching. Apart from the enlarged glands there and in his groins and axillae, nothing abnormal was found on clinical or laboratory examination. On October 18 he was pyrexial, with further involvement. On gland biopsy the case was reported as being more like Hodgkin's disease than anything else. One month later he said that he was better and that the glands had disappeared. They were, however, just palpable. The diagnosis was doubted and the question of the histology raised, but the pathologist maintained his position. A fortnight later the patient was readmitted with stridor, the glands having enlarged again. All the superficial groups were affected, but particularly the cervical. A final diagnosis of Hodgkin's disease was made and radiotherapy given. On February 17, 1953, he was readmitted with symptoms and signs of bone involvement and marrow replacement. He died three days later. *Necropsy*:—Lymph glands: abdominal mainly involved, pink or mottled red. The liver and spleen were large, the latter being soft, with an early infarct but no Malpighian bodies. *Histology*:—The spleen showed a pleomorphic mixture of lymphocytes, plasma cells, large mononuclears, occasional polymorphs and eosinophils, scanty Dorothy Reed cells, and primitive reticulum cells. The lymph nodes were similar, with some haemorrhages. The marrow showed no haemopoietic tissue but small collections of cells resembling those in the spleen. The liver showed a non-specific picture. *Comment*:—The appearances are like those of Hodgkin's disease, but are not absolutely classical.

Case 2.—A schoolboy aged 14 was admitted as an emergency case on January 2, 1952, complaining of swellings in his right groin for two weeks. His temperature was 103.8° F. (39.9° C.). He was ill and drowsy. He had marked tender enlargement of all the right inguinal glands. There was a small uninfected scratch on the right calf and no lymphangitis. Blood cultures were sterile and his white-cell count was 4,600 per c.mm. He was treated with antibiotics, but his temperature seemed to settle fortuitously. The glands decreased to about half their original size, but in August others appeared elsewhere. Section showed Hodgkin's disease. He was readmitted on November 26 with visceral as well as glandular involvement. He responded to nitrogen mustard therapy, but subsequently died at home.

Case 3.—A farm labourer aged 36 was admitted on June 7, 1952, as a case of Hodgkin's disease for a gland biopsy. His story was of malaise, night sweats, and a cough of recent onset. His temperature was 99.4° F. (37.4° C.). Most groups of glands were enlarged, and his spleen was palpable two fingerbreadths down. He had signs of collapse at the right base. Chest *x*-ray examination showed enlargement of the right hilar and paratracheal glands. After pyrexia for five days the swelling of the spleen and glands subsided along with the temperature. He was discharged with a tentative diagnosis of glandular fever in spite of a negative Paul–Bunnell test and differential white count. His general condition improved. He was readmitted with a recurrence and a remittent temperature up to 102° F. (38.9° C.). The glands had enlarged, as were the spleen and liver to four fingerbreadths. The chest *x*-ray report stated that there was "marked decrease in the glandular shadows but not complete resolution." Biopsy showed Hodgkin's disease.

Case 4.—A miner aged 50 was admitted on March 5, 1952. Eighteen months previously he had noticed lumps first on the right and then on the left side of his neck. They subsided without treatment. Four months before admission they enlarged again. With the glandular enlargement went general symptoms. He was pyrexial, with discrete enlargement of all groups of glands except the posterior cervical and the axillary. Section of a gland showed appearances more like Hodgkin's disease than anything else.

Case 5.—A housewife aged 29 was admitted on February 4, 1952. Her main complaint was of pain substernally after meals and night sweats. She was pyrexial, with epigastric tenderness but no significant glandular enlargement. Chest *x*-ray examination showed hilar lymphadenopathy. A Mantoux test was positive at 1:1,000, but her sputum was negative for *Mycobacterium tuberculosis*. Tuberculosis or reticulosis was the provisional diagnosis. Following readmission for haemoptysis on February 26, she had a large tender gland above the left clavicle. Biopsy was postponed because she developed a cold and then because the gland disappeared. Subsequent biopsy of a recurrence showed appearances more like Hodgkin's disease than anything else.

In the remaining six cases the decrease in size was not so dramatic, and in two there was a possible focus of infection.

Discussion

There is no reference to this phenomenon in most recent textbooks. Horder and McNee (1950) describe Hodgkin's disease as "characterized by painless, progressive enlargement of the lymph nodes." Cecil and Loeb (1951) make a similar statement, and say that the onset may be associated with oropharyngeal infections, but there is no proof of their connexion. Longcope (1927) states that "the correct conclusion may not be arrived at until the subsidence of the swellings (glands) with complete recovery excludes Hodgkin's disease." It was such statements as these which made our original diagnoses suspect.

Again there are few papers in which it is mentioned. Wallhauser (1933), in a review mainly concerned with pathology, merely says that he has known regression to occur. Symmers (1948), in a paper of similar nature, does not hint at it; nor does Gilbert (1939), although many varied presentations are discussed. Slaughter and Craver (1942) mention a case in which it probably occurred.

Among clinical reports, Baker and Mann (1939) and Goldman (1940) also ignore it. Middleton (1937) briefly mentions it, but without histories. This emphasis upon the progressive enlargement of the glands in Hodgkin's disease seems to be derived from Dorothy Reed's classical paper

in 1902. She, however, was faced with the problem of definition of the disease and therefore had to choose strict criteria for the cases for her studies.

As early as 1911 MacNalty recognized that there was a definite form of Hodgkin's disease associated with a relapsing fever. He noted that sometimes when the temperature became normal the spleen and glands decreased in size. This seems to have been widely forgotten in recent years, although Rolleston (1925) quotes MacNalty.

Hodgkin (1832) himself recorded a case in which the spleen and right glandulae concatenatae (cervical glands) were considerably enlarged, but "under the treatment employed these tumours, as well as that in the situation of the spleen, were at times very considerably reduced in size." This patient, Ellenborough King, was accepted by Fox (1936) as being a true example of the disease on histological grounds. The variations were probably spontaneous. Murchison (1870), who recorded the recurrent febrile episodes now erroneously accorded the eponym of Pel–Ebstein, comments on it clearly. Gowers (1879) stated that "a remarkable diminution in size of the glands may occur," and he refers to the "alternating pyrexia," thus avoiding inaccurate eponymity. Barron (1926) records a case in which the glands subsided, followed by a relapsing fever without a local recurrence.

Variation in the size of the spleen with the temperature is perhaps better appreciated. Whittington (1915) and Baldridge and Awe (1930) each recorded such a case. Jackson and Parker (1947) note that "it is not so well known that an enlarged spleen may diminish in size without any treatment whatsoever." However, they attribute diminution in size of the lymph nodes to the elimination of secondary infection, and add that their virtual disappearance should not be taken as proof that they merely represent chronic inflammation. In support, they give a history, and comment on whether the glands which decreased in size were actually involved with Hodgkin's disease at the time or not. Elsewhere they quote histories, and four more of these contain definite statements of variation in size without treatment, although the diagnosis had not yet been confirmed. Hoster and Dratman (1948) in a comprehensive review, do not refer to it in the clinical section, although elsewhere they quote it in favour of the inflammatory nature of the disease.

Whenever regression of the glands or spleen is recorded and explained, either secondary infection is invoked to account for it or it is implied that the disease may not have been present in these glands. I submit that regression of the glands may occur as part of the natural history of one form of the disease. In Case 1 the diagnosis was thought to be Hodgkin's disease from the biopsy before the decrease in size occurred. Nor was there evidence of infection. It is unlikely that several groups of glands should regress as in Cases 1 and 3 if a local septic focus is the cause. Indeed, where only one group of glands has been involved there is not always a convincing source (Case 2).

The commonest group of glands affected appears to be the posterior cervical and not the tonsillar and superior cervical. It would be reasonable to expect the latter if secondary infection played an important part (Baker and Mann, 1939). Jackson and Parker (1947, p. 67) contrast the rarity of involvement of the tonsils by Hodgkin's disease with its frequent infections. They therefore deny a direct relationship, and suggest that they serve only to light up dormant disease or to draw attention to already enlarged glands. Case 5 shows how this may occur. There was no suggestion of an infection in Cases 1, 3, or 4, while in Case 2 both groups of inguinal glands were enlarged, which would be unusual for such a local lesion.

The reason for the decrease in size is unlikely to be necrosis, as it coincides with restoration to apparently normal health, whereas patients with necrotic neoplasms are usually ill. The enlargement of the glands in Case 1 prevented a proposed further biopsy. So far as our knowledge extends, such behaviour is seen only in some of the leukaemias apart from infections.

The reason for the high incidence of this phenomenon in the series under survey is uncertain. There is nothing to suggest sex, abnormal selection, geography, or inadequate records as a reason. Whatever it is, this phenomenon, which clearly has received insufficient attention in the past, is an important feature of one form of the disease. Such an occurrence is no reason for doubting the diagnosis.

Summary

The glands in a patient with Hodgkin's disease were observed to undergo almost complete regression without treatment.

Out of 29 cases, 5 showed the phenomenon clearly and a further 6 less well.

The cursory attention that this occurrence receives in the literature is noted; there is no evidence that elimination of secondary infection, adduced as a possible explanation, is responsible.

It is submitted that regression of the glands in Hodgkin's disease, often associated with an alternating fever, is an occasional but important variant of its natural history.

I am grateful to the various consultants under whom these patients were admitted for permission to publish, especially to Dr. T. H. Boon, and to Drs. L. W. Carstairs and J. N. Walton for their advice and criticism.

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The fifth annual report of the medical officer in charge of the student health service at the Queen's University of Belfast contains an account of some student health services in the United States. The University of Minnesota, for instance, has one of the most advanced student health services in the world. It has been in existence for 32 years and is responsible for the medical care of 17,000 students. The staff consists of a director, an assistant director, 13 whole-time physicians (three of whom are psychiatrists), and 50 part-time physicians and consultants. The staff also includes a sanitary engineer and four sanitary inspectors responsible for the public health of the university campus. The service maintains its own laboratory, *x*-ray and ophthalmic departments, dental clinic, and a separate 50-bed hospital. The present hospital building was built four years ago and is magnificently equipped. The student health service is self-supporting and receives no funds from the general university budget. Each student pays a fee of five dollars a quarter, which entitles him or her to the initial medical and *x*-ray examination and four days in hospital. Fees are charged for special examinations, drugs, dental treatment, and any stay in hospital above the allotted four days. The main aim of the service is the care and treatment of the individual student during illness, and the service is used by about 80% of the student population. It is less expensive to the student than private or other hospital services.

SYMPTOMS AS A GUIDE TO ANAEMIA

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It is well known that persons with anaemia vary greatly in the degree to which they complain of symptoms. The study described below approaches the problem from the opposite angle—namely, the extent to which symptoms capable of being interpreted as due to anaemia, such as lassitude or feeling "below par," are in fact an indication of the prevalence of anaemia.

Method and Material

A total of 360 housewives, attending for miniature *x*-ray examination and found free from tuberculosis, accepted the offer of a haemoglobin test. They were asked to answer the following questions:

Do you feel fit? .....
Average? .....
Below par? .....
Do you suffer from:
Breathlessness? .....
Poor appetite? .....
Always feel tired; lack of energy? .....
Swelling of ankles? .....
Do you need to take a laxative once a week or more?

It was realized that the questions were of a leading nature, but they were asked before the subject knew the result of the test, and were applied to all subjects without bias. The questions were not intended to include all the symptoms of which anaemic subjects are said to complain. The question on laxatives was posed so as to provide an objective index of the constipation which may accompany anaemia.

Haemoglobins were tested by the doctors, to whom acknowledgment is made above, using oxyhaemoglobin in Grey–Wedge photometers. Finger-prick blood was used. Each operator calibrated herself on an average once per ten determinations by means of the invaluable samples provided by the M.R.C. haemoglobin standards scheme (Dr. I. D. P. Wootton).

Haemoglobin Levels in Housewives who Complained, or Did Not Complain, of Certain Symptoms

	No.	Mean Hb (% Haldane: 100%= 14·8 g./100 ml.)	% Below 83%	% Below 73%
Below par	49	91·10	12·2	10·0
Average	172	89·70	16·3	5·8
Fit	127	89·95	12·6	4·7
Swelling ankles	73	89·80	20·5	4·1
Not „ „	277	90 08	13·0	6·1
Breathless	134	90 24	16·4	9·0
Not „	225	89·82	13·3	4·0
Always tired	153	90·04	15·7	7·8
Not „ „	202	90·00	13·9	4·5
Poor appetite	43	90 21	9·3	7·0
Not „	313	90·00	15·0	5·4
Constipated	104	89·31	19·2	5·8
Not „	248	90·42	12·5	5·6
Fit, not always tired, *not* breathless	94	90·20	13·8	4·3
Below par, always tired, breathless	31	90·58	12·9	12·9

Where a reply was equivocal no entry has been made. Hence the difference in total numbers in each division. The level 83% was selected because at this level prospective blood donors are refused by the Ministry of Health Transfusion Service.

Results

The Table shows that there was no difference in mean haemoglobin level between those that did and those that did not complain of these symptoms. Those whose haemoglobin level was below 73% were present in rather larger proportion in the group which complained of symptoms; but the differences were not greater than could occur by chance.

Discussion

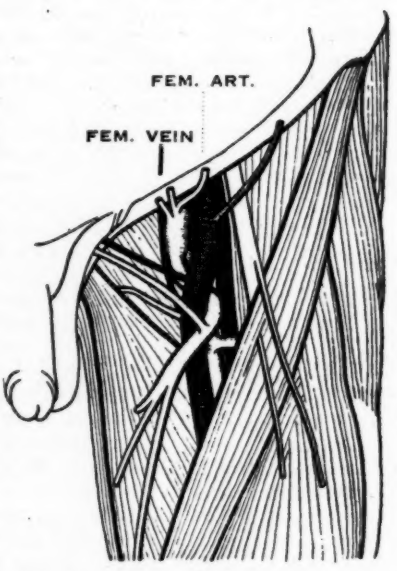
The symptoms that we are dealing with are common today, as indeed the number of positive replies to our questionary suggests. Whether this has always been the case it is impossible to say; and, in any event, this is less important than to know the cause. Anaemia, to us, seemed to be one of the possible causes in practice, but it is clear from the analysis of our data that this is in fact not so.

Medical Memoranda

An Important Anomaly of the Long Saphenous Vein

Ligation of the superficial or deep veins of the lower limb is so commonly practised that the following anomaly of the long saphenous vein discovered in the course of routine laboratory dissection merits description.

Ascending through the femoral triangle the long saphenous vein crossed in front of the femoral artery to reach its lateral side 4 in. (10 cm.) below the mid-inguinal point. It then passed backwards and medially behind the artery to end in the femoral vein 2½ in. (7 cm.) below the mid-inguinal point—that is, about 1 in. (2.5 cm.) lower than usual. Where the long saphenous vein crossed in front of the artery the two vessels were firmly bound together by fibrous tissue. Thereafter the vein was intimately related to the artery below the origin of the profunda femoris branch, and thus it described a spiral course round the lateral side of the femoral artery (see Fig.). The level at which the vein pierced the deep fascia could not be determined, as the dissectors had removed the fascia in an attempt to elucidate the abnormal relationship. However, since the femoral artery is always beneath the deep fascia, it is likely that the long saphenous vein perforated that fascia at or before the point where it crossed in front of the artery. The femoral vein lay on a more posterior plane than the femoral artery immediately below the inguinal ligament, and the superficial circumflex iliac and the superficial epigastric veins ended in it.



The long saphenous vein passing spirally round the lateral side of the femoral artery.

The practical importance of this anomaly is clear. A point 1½ in. (3.8 cm.) below and lateral to the pubic tubercle, the standard guide to the middle of the saphenous opening (fossa ovalis), was found in this case to be opposite the

femoral vein just as it appeared on the medial side of the femoral artery. Using this surface marking, the surgeon intending to resect the terminal part of the long saphenous vein would not come upon that structure in this case. Instead, on tracing the superficial circumflex iliac and superficial epigastric veins to their termination, he would pass imperceptibly beneath the deep fascia, cribriform in this region, into the plane of the femoral vessels. If the vessel which then presented itself was the femoral vein, this might be ligated in error. On the other hand, if the dissection were carried low enough to encounter the long saphenous vein, the close relationship of this vessel to the femoral artery might result in the inclusion of both artery and vein in the ligature. That the femoral artery has been injured in the course of Trendelenburg's operation, occasionally with subsequent loss of the limb or death, is beyond doubt.

Luke and Miller (1948) cited three certain cases and one probable case of ligation of the femoral artery. McPheeters (1945) described two cases of ligation of the femoral artery, and in one of these the femoral vein was also tied. At least three cases have come to my notice in this country in which either injury or ligation of the femoral artery occurred during this operation. For obvious reasons it is difficult to get details of the operative findings, but it is possible that the anomaly described above may have been present in some of these cases.

A somewhat similar course of the long saphenous vein was described and illustrated by von Lanz and Wachsmuth (1938). It was also depicted in Fig. 5 of an article by Anson and McVay (1938), so that it cannot be exceptionally rare. No mention was made of its significance in either of these texts.

Whatever the explanation of the surgical errors associated with Trendelenburg's operation it is obvious that the surgeon should be aware of the deceptive variation described in this report. The technical difficulties which it presents are slight. The real danger lies in not knowing that such a condition may exist.

My thanks are due to Professor D. R. Dow for assistance in writing this report.

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Two Cases of "Novalgin" Agranulocytosis

Numerous reports of the occurrence of agranulocytosis following the administration of "novalgin" and other drugs containing amidopyrine have been published (Kracke, 1931; Plum, 1934; Stenbeck, 1935; Benjamin and Biederman, 1936; Moloney and Vidoli, 1943; Kneedler, 1946). Now that these drugs have been put on the Fourth Schedule of the Poisons List, and the danger of their use is more widely appreciated, cases such as those recorded below should become rare.

CASE 1

A female domestic worker aged 70 was admitted as a suspected case of diphtheria in July, 1950. For three weeks previously she had been taking novalgin tablets (which she obtained direct from the chemist) for rheumatic pains, the exact dose being unknown. Two days before admission she had chilly sensations with malaise, and the next day a sore throat and difficulty in swallowing.

On admission she was found to be well nourished but not fat, and was obviously very ill, with stertorous breathing and a hoarse nasal-sounding voice. Both tonsils, uvula, and soft palate were covered with patchy exudate, greenish yellow in colour, and on the left tonsil it was becoming black, indicating early gangrene; fetor was pronounced and an icteric tinge was visible on the conjunctivae. The tonsillar lymph nodes were moderately enlarged. The blood pressure was 135/70. Blood count: Hb, 80%; red cells, 3,800,000; white cells, 750 (lymphocytes 100%, no granulocytes). From the throat swab *Streptococcus viridans* only was grown. Penicillin, 500,000 units, and pentnucleotide, 10 ml., were given intramuscularly immediately on admission, but the patient died three hours afterwards, before arrangements for a transfusion of fresh compatible blood could be made. Necropsy revealed a superficial pharyngeal necrosis extending from tonsils to epiglottis and haemorrhagic congestion and oedema of the lungs with subpleural and subpericardial haemorrhages.

CASE 2

A female domestic worker aged 68 was admitted to hospital with tonsillitis and pneumonia in May, 1952. In the previous month she saw her doctor on account of painful stiff joints, when novalgin was prescribed in doses of 2 tablets, each containing 5 gr. (0.32 g.), three times a day; over a period of three weeks she had taken a total of 90 tablets, when she became febrile and weak with sore throat, dysphagia, and hoarseness. Novalgin was discontinued at once, and two days later she was given sulphamerazine, a total of 30 g. in five days, without apparent response, and was admitted to hospital.

She was obese, pale, and obviously ill, with hurried noisy breathing; her temperature was 101° F. (38.3° C.), pulse 120, and respirations 30. Exudate covered most of the tonsillar surfaces and spread to the uvula and soft palate without underlying ulceration. The associated lymph nodes were enlarged and tender, and moist sounds were heard at both lung bases without evidence of heart failure. Blood count: Hb, 78%; white cells, 2,000 (neutrophils 3%, lymphocytes 90%, monocytes 7%). Some of the lymphocytes were atypical early forms. A heavy growth of *Str. viridans* was obtained from the throat swabs, but haemolytic forms were not present. Crystalline penicillin, 1,000,000 units daily, was given for seven days, with amelioration of the symptoms and rapid disappearance of the exudate. Immediately thereafter she received 9.5 g. of chloramphenicol over four days on account of persisting bronchitis, to which she was known to be prone. Two days after penicillin was started the white cells numbered 3,100 (neutrophils 10%, lymphocytes 78%, monocytes 12%), and two days later the count was almost normal, subsequent recovery being uneventful.

COMMENT

Despite the similarity of the two patients in respect of age, occupation, and physical state, and probably also of the amount and duration of ingestion of novalgin, the clinical differences in the character of the disease—in the one brief and rapidly fatal, and in the other, over a week and mild with prompt resolution—are impressive, suggesting that idiosyncrasy may be the most important aetiological factor. There was no history of previous ingestion of the drug, although this could not be eliminated completely, especially in Case 1.

The absence of recognized respiratory pathogens, such as haemolytic streptococci, suggests that the faucial angina is a degenerative or allergic rather than an inflammatory condition, and therefore unlikely to respond to penicillin. Alternatively, *Str. viridans* may, under particular conditions, become pathogenic to the respiratory mucosa, as has been long suspected in association with virus invasions. Aureomycin therefore seems to be the antibiotic of choice, as chloramphenicol has been shown capable of causing both agranulocytosis and aplastic anaemia. Sensitivity tests are probably essential in severe cases to find the correct antibiotic.

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Reviews

SIGMUND FREUD

Sigmund Freud—Life and Work. Volume 1—The Young Freud, 1856–1900. By Ernest Jones. (Pp. 454, illustrated. 27s. 6d.) London: The Hogarth Press. 1953.

The author is the oldest colleague of Freud still alive. It was due to him that Freud spent his last months peacefully in this country following his rescue from Nazi-invaded Vienna. In this first volume of three Freud's life to the age of 44 is described. By 1900 Freud had established his basic concepts—the importance of unconscious mental life, the beginnings of sexuality in infancy, the value of "free association" and dream life, both for the therapy of neuroses and as a method of investigating psychic development.

Not only psychiatrists but all those who enjoy the story of the trials and triumphs of physicians will be fascinated by this book and the promise of the two further volumes to come. Dr. Jones has added to his laurels as a clear expositor. Rarely has a physician been so lucky in his biographer or a medical biographer in his subject. It is difficult to make comparisons, but one thinks of Cushing's much-read life of Osler and Pearson's unfortunately little-read life of Galton. Galton, Osler, and Freud were all clear and voluminous writers. Unfortunately, at one time Freud destroyed much of his previous writings, but Ernest Jones has had access to many family letters, perhaps the most significant being the 1,500 love letters sent by Freud to his future wife during their four years' engagement previous to marriage when he was 30. Freud's letters to his friend Fliess during the 'nineties, when he was gradually leaving neurology for psychology, have been preserved (they will soon be published in an English translation) and give a vivid picture of the doubts and mental anguish of a pioneer. Gradually his independence emerged, and he sought collaborators as critics rather than the opinions of those who did not seek confirmatory access to the facts he had discovered.

The author's stated aim is the hope of elucidating something of the processes in Freud's mind and the experiences in his life which led to his discoveries. The scanty details about Freud's childhood and adolescence which are available are partly compensated for by the greater knowledge of his medical studies until graduation at 25 and his career as a neurologist. Apart from his interest in cocaine as a treatment for depression—which nearly led to his discovering its use as an analgesic—his early years as a physician were typically those of one who wished to become a consultant neurologist. This period ended with his most important neurological publication "Aphasia" in 1891, which did not attract the attention in this country it deserved. In it he strongly supported Hughlings Jackson's genetic views. His numerous neurological publications established his reputation in this field as a hard worker and a close thinker, but only in his work "Aphasia" was there a hint of the genius which was to appear.

During the 'nineties the work that established psychoanalysis was done almost alone. His early contact with Breuer was, of course, important. But he soon had to test his developing hypotheses without the help of others. In 1889, replying to Meynert's criticism of his interest in hypnosis, he wrote: "Respect for greatness, especially intellectual greatness, belongs to the best qualities of human nature. But it should take second place to respect for facts. One need not be ashamed to admit when one sets aside reliance on authority in favour of one's judgment gained by a study of the facts."

The publication in 1893 of his and Breuer's experiences of transference phenomena in hysteria led to the first note of his work in this country, F. W. H. Myers giving a good account of it in the *Proceedings* of the Society for Psychical Research in June, 1893. His 1895 "Studies in Hysteria" were favourably reviewed by Mitchell Clark in *Brain* in 1896. During the period 1892–6 the method of free association gradually developed, and was freed from hypnosis, suggestion, urging, and questioning. In 1898 he began to realize the importance of the connexion betwen infantile and pubertal sexuality. From 1897 his own self-analysis continued.

In the 'nineties the beginning of the resistance and reaction to his views began—not so much to his view of unconscious mental life, which was generally accepted, but to the content he discovered. To Freud the unconscious gradually became an inner reality deep to consciousness just as real as the outer reality beyond that which our senses give access to. From the beginning of his interest in psychology he manifested his wish to understand normality. In 1882 he had written of his uncanny feeling when he could not understand someone in terms of his own experience. The passage from physiology to psychology meant much more to Freud than a change in intellectual outlook. It betokened a need to reach towards the depths of his own being, which for many years had been covered over. His long self-analysis was the first of many that have followed in physicians who are unsatisfied unless they can attempt to understand the sufferings and delights of others in terms of their own.

Freud emerges from this book as the complex man he was: with his scientific industry, his love of family, his love of travel and pursuits outside medicine, and his neurosis. The reader will be left baffled but thrilled. This is the lot of those who try to comprehend genius.

W. CLIFFORD M. SCOTT.

ARTERIOSCLEROSIS

Arterioesclerosis. By Dr. José Froimovich. (Pp. 218: illustrated. No price given.) Valparaiso, Chile.

This book, which is described as a clinical and experimental study of arteriosclerosis, comes in Spanish from Valparaiso. The term "hardening of the arteries," which is the exact translation, is in many ways unsatisfactory. It may refer to one or more of several distinctly different diseases. In this book the discussion of the pathogenesis refers to atherosclerosis or atheroma. It ranges over a wide field, rather too wide perhaps. At times other forms of arterial disease come into the discussion, so that the text becomes rather confusing. Many authors are quoted, but there is no summary or synthesis of views. In the account of morbid anatomy the reader is again confronted with a great many references from various authors. The experimental work is shown in a number of photomicrographs, but these are far from clear and do not show much detail. There are descriptions of the results of keeping rabbits on diets containing much cholesterol; the author claims that this leads to the development of atheroma; but he thinks that iodide of potassium checked the formation of the deposits. Then comes a chapter on the symptomatology of common disease. He gives some description of cardiograms, but no tracings are shown; his approach to this important subject is hardly up to date. He advocates propyl thiouracil in treating angina pectoris.

Although this book contains a large amount of work cited from many writers, the author does not discuss it well; there is a lack of correlation, sifting, and criticism. He leaves the reader without any clear idea of what he really thinks, and in some confusion about the whole subject.

TERENCE EAST.

MANUAL OF PSYCHIATRY

A Manual of Psychiatry. By K. R. Stallworthy, M.B., Ch.B. Second edition. (Pp. 314. £1 10s.) Christchurch, New Zealand: N. M. Peryer. 1953.

The writer of the foreword to this volume commends it to all who seek a soundly based, common-sense knowledge of modern psychiatry. The author achieves this objective only in part. The book will not interest the experienced psychiatrist, and the psychiatrist in training may find it rather fragmentary. But the psychiatric nurse will profit by reading the chapters on physical methods of treatment and special

nursing procedures. The chapter on the neuroses contains some recommendations which could scarcely be described as soundly based. We read that it is relatively uncommon for an anxiety state to require expert psychiatric treatment. Where it does, an effort should be made "to unmask the underlying complexes," and, should this fail, leucotomy may be advised. Psychotherapy is not much in favour. The doctor who has neither time nor patience to listen to the involved story of his patient should "refer the person to some colleague who has." The superficial references to the work of Freud and Jung suggest that the analysis of the unconscious occupies a lowly place in the treatment of psychiatric illness. Physical methods of treatment, on the other hand, receive considerable attention and, by implication, are the main concern of the psychiatrist. Psychiatry is a complicated subject, and it is probably impossible, without oversimplification, to summarize its essentials in a manual designed as "a practical guide for practitioners and students of psychiatry."

E. A. BENNET.

SCIENTIFIC LANGUAGE

The Language of Science: Its Growth, Character, and Usage. By Theodore H. Savory. (Pp. 184. 10s. 6d.) London: André Deutsch. 1953.

The object of scientific prose is to convey information as clearly as possible; for this reason, ordinary words used for scientific purposes have to be specially defined, and many words have to be coined to denote things and relationships outside ordinary experience. To this extent one can say that there is such a thing as scientific language, though it is possible to exaggerate its importance; and scientific authors probably think of themselves as writers of English or other languages also used by non-scientists. It would perhaps be better to speak of a scientific vocabulary, since grammar is the same for all users of a language. This book is a collection of essays on various aspects of scientific language. The author writes on such topics as technical terms and their derivation and date of appearance, the object of scientific writing, the translation of scientific literature; and the value of foreign languages to the scientific worker. He has been a schoolmaster for over 30 years, which no doubt explains his heavily expository style and tendency to labour the obvious; much of what he has to say is in fact common knowledge, in universities at any rate. The different problems of translators of poetry and scientific prose are well discussed, but scientific translation is more difficult than the author allows; the scientific translator needs as strong a grasp of idiom as the translator of verse. The author thinks that the university student of science has no time for interests outside his work, and we can only hope his sample was not representative.

The book is addressed to philologists and scientists, but its strongest appeal will probably be to schoolmasters and general readers with an interest in science.

RAYMOND WHITEHEAD.

DICTIONARY OF MIDWIFERY

A Dictionary of Midwifery and Public Health. By G. B. Carter, B.Sc., S.R.N., S.C.M., and G. H. Dodds, M.D., F.R.C.S., F.R.C.O.G. (Pp. 686; illustrated. 25s.) London: Faber and Faber Ltd. 1953.

This is more than a dictionary—it is an encyclopaedia. The greater part of the book is devoted to the definition of obstetric and other medical terms and concise and accurate descriptions of a wide variety of well-chosen topics. The other part is on public health and administration.

The book is intended for midwives both for reference and for study, but the dictionary part will be welcomed also by medical students and hospital administrators, and even a reviewer may be forgiven, I hope, for forgetting the task in hand and losing himself in the neat and instructive articles in this comprehensive dictionary. The many excellent line drawings have been executed by Miss P. Forman with artistic skill and baptismal patience. I recommend unreservedly the dictionary part to all associated with obstetrics.

The smaller part on public health and administration is constructed on somewhat similar lines. Here, too, are many interesting and informative articles, but unfortunately this part is marred by a number of errors and misleading statements. For example, the Ministry of Housing and Local Government receives its correct title under that heading, but elsewhere it becomes the Ministry of Local Government and Housing, and, again, the Ministry of Local Government and Planning. And the statement that "It is usually agreed in Great Britain that the trained hospital almoner is the medico-social worker in clinic and hospital and the health visitor in the home" will not commend itself as either fact or opinion to the thousands of health visitors working in hundreds of local authority clinics in addition to their work in the home.

The whole volume would be improved by eliminating the section on public health and administration altogether, or, better still, by careful revision raising it to the standard of the main part consisting of the excellent dictionary of midwifery.

C. METCALFE BROWN.

THE DERMATOPHYTES

Dermatophytes. By Dr. Jean Obrtel. (Pp. 44; 196 coloured plates and 59 photographs. No price.) Prague: Editions Médicales.

This book presents a wide selection of beautifully executed coloured plates of dermatophyte cultures grown on standard Sabouraud media at room temperatures and an equally wide selection of good clinical photographs of the lesions caused by dermatophytes. But its practical value to the clinician and medical mycologist is vitiated by the author's adherence to the outdated classification instituted by Sabouraud. This classification is based chiefly on host–parasite relationships and on gross cultural features and does not represent the natural affinities between the various members of the dermatophyte group. The lesions caused by dermatophytes are well known to vary considerably, and similarly their gross cultural features, as is indeed so well demonstrated in this book. A classification based on such variable criteria is of doubtful value for purposes of identification and therefore defeats its own object. The classifications of dermatophytes most widely used in France, Belgium, Great Britain, and America are all based on microscopic morphological criteria presented by these organisms in culture, thus bringing them into line with the taxonomic treatment of other groups of fungi.

Some surprising mycological statements appear in the text—for example, "Le groupe Microidon comprend les dermatophytes du type ectothrix caractérisés par de *grandes spores*" (italics mine); and further on the same page, in reference to Sabouraud, "Il différencie dans le cinquième groupe les *mucorinées* dites Mégasporon en deux autres groupes indépendants" (italics mine). These are probably due to insufficient proof-reading and are such obvious errors that they are not likely to mislead at any rate the medical mycologist.

Some notes on distribution, epidemiology, clinical features, and therapy are included. While this information is in some cases based on insufficient data, it provides for workers west of the Iron Curtain an interesting documentary of local conditions as regards the dermatomycoses. The book is elegantly and sumptuously produced, but it is to be regretted that its artistic merit outweighs its scientific value. There are numerous typographical errors in the references to articles in the English language.

C. J. P. LA TOUCHE.

From the fact that the 7th edition (1953) of R. W. Fairbrother's *Textbook of Bacteriology* (Pp. 492; 20s. London: William Heinemann Medical Books) is, including reprints, its 18th issue in 16 years, it may be gathered that this work has found favour. The principal changes in this edition are in the chapters on chemotherapy and virus diseases.

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KIDNEY TRANSPLANTATION

The transplantation of kidneys is perhaps the most ambitious enterprise that has yet been undertaken in the surgery of tissue and organ replacement. Although the kidney is a firm and compact organ, with a single chief arterial input and venous outflow, and is an organ which seems not to need a nerve supply for its continued working, the obstacles to its successful transplantation are by no means merely technical. With rare exceptions—one of them described by Michon and his colleagues[1]—grafts of kidney that are to be clinically useful must be homografts—that is, they must be grafts transplanted from one human being to another or between animals of the same species. In addition, therefore, to all the technical and physiological difficulties of transplantation are all the immunological impediments arising from the fact that the tissues of one individual provoke a highly efficient, if teleologically uncalled-for, defence mechanism after transplantation to the body of another.

The experimental work of Dempster[2,3] and of Simonsen[4] and their respective colleagues on dogs has given ground for believing that these immunological difficulties are of two kinds. First, there is the reaction of the host upon the graft, which both writers believe to be similar in all essentials to that provoked by homografts of skin—that is, a kind of immunological reaction. If that were the whole story the outlook would be grave but not desperate, for the problem of abolishing reactions of this kind has already been solved for laboratory animals,[5] although by methods which, in their existing form, have no clinical application. But both Dempster and Simonsen have described certain histological appearances (confirmed, in Dempster's work, by irradiation experiments) which suggest, unfortunately, that a second factor is at work—the reaction of the kidney homograft against its host. This possibility, although it still requires a formal experimental proof, is entirely plausible, and its recognition is one of the most important contributions to the theory of tissue transplantation immunity that has been made in recent years. There is no reason at all why a graft, if it contains antibody-forming cells, should not respond to the antigenic matter entering it from its host. When two animals are in parabiotic union, each is graft and each host, and Simonsen believes that the kidney homograft is best thought of as a parabiosis of unequal partnership. With homografts of many types—for example, of skin or cancerous tissue—a reaction of graft against host is either absent or of little importance; skin homografts, for instance, will survive indefinitely after transplantation from members of an inbred line of mice to the progeny of a cross between that inbred line and another. As every geneticist knows, such a situation is one in which the host does not react against the graft, for the graft contains no antigens not also present in the host; but there is nothing to stop the graft reacting against the host if it is immunologically qualified to do so. Neither Dempster nor Simonsen have had the good fortune to work with highly inbred dogs, perhaps because no dogs of sufficient genetic uniformity exist. It is not therefore possible to weigh up the relative importance of host-against-graft and graft-against-host reactions in homografts of kidneys. The former type are indeed entirely competent to account for the failure of kidney homografts as such, but the question is: if the reactions of the host can be subdued or abolished—it can surely be only a matter of time before they are—will the converse reaction, of graft against host, be in itself sufficiently severe to cause kidney homografts to fail?

So much for the immunological hazards of kidney transplantation. Superimposed on them are the technical and physiological disabilities of the transplantation itself. Autografts of whole kidneys are, in general, of two kinds: these are the isotopic (or orthotopic), in which the graft is transplanted into the position formerly occupied by a kidney, and the heterotopic, in which it is caused to derive its external blood supply from, perhaps, the iliac or carotid arteries. The orthotopic graft enjoys certain neighbourly relationships that are denied it elsewhere. For instance, it has long been known that removal of one of the adrenals increases the outflow of urine from the kidney of the same side. Dempster and Graber[6] are satisfied that this alteration of function is not to be attributed to splanchnic denervation, and they think it possible (as Cow did some forty years ago) that the adrenal exerts a direct hormonic influence via the lymphatics upon the kidney of the same side. How-

[1] Michon, L., *et al.*, *Presse méd.*, 1953, **61**, 1419.
[2] Dempster, W. J., *British Medical Journal*, 1951, **2**, 1041.
[3] —— *Brit. J. Surg.*, 1953, **40**, 447.
[4] Simonsen, M., *et al.*, *Acta path. microbiol. scand.*, 1953, **32**, 1.
[5] Billingham, R. E., *et al.*, *Nature (Lond.)*, 1953, **172**, 603.
[6] Dempster, W. J., and Graber, L. G., *Acta med. scand.*, 1953, **146**, 411.
[7] —— and Joekes, A. M., *Quart. J. exp. Physiol.*, 1953, **38**, 11.
[8] *Acta med. scand.*, 1953, **147**, 99.
[9] Ibid., 1953, **144**, 360.
[10] Lawler, R. H., *et al.*, *J. Amer. med. Ass.*, 1950, **144**, 844.
[11] —— Ibid., 1951, **147**, 45.

ever that may be, a dog's kidney transplanted to the neck works, and may work permanently, but it does not work quite normally. Dempster and his colleagues[7 8] have consistently recorded, among other shortcomings, a rapid and permanent deterioration of the graft's power to concentrate urine, the specific gravity of which falls to a fairly constant level of about 1012 (the normal range in dogs is 1035–1050). This deterioration was not corrected by the removal of the dog's remaining normal kidney. But removal of the normal kidney did restore to its original value a total urinary output which had fallen to a half or less in the period beginning from about a month after transplantation. A toxic syndrome which sometimes develops after a period of useful working in kidney autografts[9] is probably due to infection consequent upon a vascular accident, since it usually yields to the administration of terramycin; but Dempster finds no ground for believing that the administration of any antibiotic can prolong the life of a kidney homograft as such.

Dempster gave an account of his interpretation of the behaviour of kidney homografts at a symposium on immunological problems of tissue grafting held at the Royal Society of Medicine on April 6, paying special attention to the histopathological evidence of the reaction of graft against host. It is against the background of these systematic physiological and immunological researches that we must appraise the occasional attempt to make use of kidney homografts in clinical practice.[1 10 11] For reasons that are not yet clear the human being is, in a purely quantitative sense, more tolerant of homografts of all kinds than are most domesticated animals, and kidney homografts in human beings may therefore sometimes last long enough to raise hopes which later suffer a tragic disappointment. Kidney homotransplantation cannot at present be carried out in human beings with any theoretical expectation of success. The problems of tissue-transplantation immunity are not likely to yield to anything but prolonged, systematic, and fundamental research, and it should be a cause for some satisfaction that the homografting of kidneys has in recent years been made the subject of research of the concentration and skill required.

THE PROMOTION OF WORLD HEALTH

World Health Day, April 7, was celebrated in London at a meeting, addressed by Dr. M. G. Candau, Director-General of the World Health Organization, and by Mr. Walter Elliot, M.P., a former Minister of Health. The theme of the meeting was the vital part played by the nursing services, and a letter was read from the present Minister of Health expressing appreciation of the importance of nurses in all branches of the National Health Service. On the following day Dr. Candau spoke at the Royal Society of Medicine and showed a film illustrating the work of W.H.O. His visit to London coincided with the publication of his annual report[1] to the World Health Assembly, which meets in Geneva in May. The report mentions that there were about 350 W.H.O. projects in 74 countries last year. The greatest number of these were proceeding in south-east Asia, and the next largest groups were in Europe, the Americas, and the Eastern Mediterranean, with 60 or 70 enterprises in each region. W.H.O.'s activities in Africa were relatively few in 1953, but they extended from public health education in Liberia to the supply of medical school equipment in Kenya and malaria control on the Congo. India received help in nearly 30 separate undertakings, from assistance for a school of nursing in Calcutta to a paediatric unit in Madras General Hospital, and from a campaign for B.C.G. vaccination in Delhi State to the establishment of a school of physiotherapy in Bombay. In the Eastern Mediterranean the projects ranged from a public health laboratory in Jerusalem to an eye diseases seminar in Cairo; and in Europe, from the setting up of a child guidance clinic in Dublin to venereal diseases control in Istanbul. Another feature of the European work of the Organization last year was inter-country programmes—for example, France and the United Kingdom continued a three-year pilot study to determine the kind of health visitor best suited to meet health and welfare needs, and they collaborated also in a study of the effects of separating the child from its mother in the early years of life. Many European countries also joined together in conferences and training courses.

As these projects are developed they seem to have a sharper definition than in earlier years. W.H.O. is not a rich uncle distributing largesse among impoverished nephews. Its purpose is to stimulate regional and local effort so that eventually there may be in every country and territory a band of trained and competent workers to man the health services. In the distant future when that is accomplished W.H.O. will have a different role to play. Meanwhile, as Dr. Candau rather sadly remarked at the World Health Day meeting in London, the funds available from technical assistance sources are liable to fluctuate. In order that the work of the Organization will not suffer, the World Health Assembly at its gathering in Geneva next month is to be asked to increase the effective working budget from the

[1] *The Work of W.H.O. in 1953*, 1954. Geneva.

previous year's figure of 8,500,000 dollars to 10,300,000 dollars. This amount, Dr. Candau said, was needed to enable them to carry out, without interruption, their planned health activities in 117 countries and territories in 1955. He added that the United Kingdom was the second largest contributor, after the United States, to the funds of W.H.O.: at the present moment the United Kingdom contribution to W.H.O. amounted to 1½d. per head of the population per year. If the budget was increased by the desired amount the cost to every person in the United Kingdom would be one halfpenny a year more. It is unfortunate that a number of countries are in arrear with their contributions, and that there is a phalanx of inactive members behind the Iron Curtain, but even with these disabilities W.H.O. achieved much to be proud of in 1953 and will undoubtedly continue to play a central part in the work of improving environmental conditions throughout the world.

THE PROPHYLACTIC EGG

With the coming of Easter and springtime we welcome both the chocolate eggs in the shops and the renewed determination of hens to start laying real ones. Unlike the chocolate variety or the somewhat rarer cardboard type enclosing a string of pearls, real eggs contain choline, and, if Wallis's theory about egg lack in rheumatic fever turns out to be correct, the sudden decrease of rheumatic fever after the peak maximum incidence of April[1] and its low incidence during summer might be due to Easter and its effect on the domestic fowl. Though this particular fancy is not included in the chain of possibilities elaborated by Wallis, he postulates that a deficiency of eggs during childhood (among other factors) leads to rheumatic fever. His argument is that low egg intake means low choline intake, and, since choline is necessary for serum phospholipid synthesis and cannot itself be synthesized, this may in turn lead to low phospholipid serum levels. Since serum phospholipid is one of the normal serum factors which inhibits the streptococcal exotoxin streptolysin S,[2] and since rheumatic fever is associated with streptococcal infection, the possibility exists that rheumatic fever might be conditioned partly by egg intake. This is a long and tenuous chain of reasoning, but it can be tested at various points, and Wallis provides some information at two. First, by retrospective inquiry among a group of 184 adult or adolescent patients with rheumatic heart disease and a group of normal subjects of similar economic status, he establishes[3] that 41% of the former believe they ate few eggs in childhood as against 16% of the latter. Ten per cent. of the cardiac group disliked eggs as against 5% of the controls. How significant this is we do not know. Such retrospective inquiries are difficult to conduct free from bias (although attempts were made to eliminate this) and even more difficult to interpret. His second contribution is a study of serum phospholipid levels at various ages in 146 normal subjects and in 178 patients with inactive rheumatic heart disease.[4] This substance rises from a normal mean level of 8.2 mg. per 100 ml. in children aged 3–12 to 9.7 mg. per 100 ml. in adults aged 20–39, but with a great deal of scatter in the readings. In the cardiac group no mean values are given, but it is stated that the serum level was below normal average in two-thirds, tending to be lower in those with multiple attacks or of a severity great enough to need digitalis. Although Wallis found that 10.2% of 184 rheumatic heart disease patients and 4.6% of 1,380 normals disliked eggs, no information is given of the serum phospholipid level of the egg lovers and the egg haters.

Previously Coburn and Moore[5] had reported a poverty of eggs and other materials in the diet of rheumatic children and had supplemented the diet of thirty convalescent rheumatic children with the equivalent of four egg-yolks a day. Recurrences occurred in 7% of this group, compared with 38% of thirty children whose diet was not supplemented. No further studies have been described in detail, though Coburn has reported[6,7] briefly that 8–10 yolks daily prevented rheumatic relapses after group-A streptococcal infection in children who had previously had rheumatic fever.

The best hypotheses are the simplest. All current theories about the aetiology of rheumatic fever are complicated, and none more so than that recently suggested by Long[8] on a basis of cabbage, thyroid, ascorbic acid, and tuberculin allergy in the guinea-pig. So long as a clear distinction is made between observation and speculation we should welcome theories if they are founded on fact and lead to the discovery of more facts. The egg theory might be described as "good in parts." Although support for it is meagre, we cannot afford to neglect any clue to the nature of the streptococcal role in initiating rheumatic fever. But the enthusiastic clinician might pause before loading his patients with eggs to prevent rheumatic fever lest he speed them on the way to atherosclerosis and coronary disease.

DEXTRAN AND NEPHROTIC OEDEMA

Recently two new therapeutic agents have been used in the treatment of nephrotic oedema. They are cation-exchange resins and dextran. So far, more of the clinical trials have been with cation-exchangers, but now the first studies on the effect of dextran have been published,[1,2] and it is beginning to be possible to assess its usefulness in this syndrome. The essential principles by which resins and dextran work are quite different. Cation-exchangers increase the loss of sodium from the body, while dextran increases the osmotic pressure of the plasma and so attracts idle water from the oedematous parts, and possibly hinders tubular reabsorption of water in the kidneys.[1]

[1] Wilson, May G., *Rheumatic Fever*. Oxford University Press, London. 1940.
[2] Humphrey, J. H., *Brit. J. exp. Path.*, 1949, **30**, 345.
[3] *Amer. J. med. Sci.*, 1954, **227**, 167.
[4] Ibid., 1954, **227**, 171.
[5] *Amer. J. Dis. Child.*, 1943, **65**, 744.
[6] Ibid., 1945, **70**, 348.
[7] *J. Amer. diet. Ass.*, 1950, **26**, 345.
[8] *Lancet*, 1954, **1**, 529.

Elsewhere in this issue of the *Journal* Drs. A. W. Mollison and J. B. Rennie report their experience of treating nephrotic oedema with intravenous infusions of dextran. Dextran was given on 81 occasions to eight patients. All were at rest in bed, on restricted salt intake, and a moderately restricted fluid intake. Seven patients received a high and one a normal protein intake. The dextran was used in a standard commercial 6% salt-free preparation, and three 10% salt-free preparations of large, medium, and small molecular size. Diuresis and delivery of the oedema occurred with all these preparations, regardless of molecular size or concentration, but the effect lasted longest with the large molecular preparation. In all cases the oedema reaccumulated. Dextran had no adverse influence on renal function. Toxic reactions to infusion were noted in all cases, and consisted of severe headaches, occasional nausea and vomiting, and fever; two patients developed transient hepatic enlargement; one patient developed fever, dyspnoea, cough, and scanty rales at the lung bases after the fourth infusion of small-molecule dextran, and another developed the same symptoms though less severely with a similar preparation. The more severe reactor of these two also showed signs of the greatest increase in blood volume of any of the patients in response to the infusion, and this occurred at the time of his reaction; skin tests for sensitivity to dextran were negative. The authors thought that the reactions they encountered were not allergic so much as due to overloading of the circulation, and they found that slowing the rate of infusion reduced the severity of the reaction.

It is interesting that subsequent courses of dextran after the first were effective in producing diuresis in this series of cases. Olive *et al.*[2] found that in two of the twelve children with nephrotic oedema whom they treated the second course of dextran failed to cause diuresis even though the first had been quite effective. On the other hand they noted toxic reactions in only three of their cases, the reactions being correlated with the use of a preparation of high molecular weight and with frequent molecular branching. Kabat and Berg[3] noted that dextran given to healthy humans was antigenic, and Kabat, Turino, and Tarrow[4] have shown that cutaneous sensitivity to dextran was statistically correlated with the occurrence of systemic reactions to subsequent intravenous infusions. Apart from the reactions of an antigenic or haemodynamic type Mollison and Rennie draw attention to a hitherto unremarked complication to its therapeutic use. Two of their patients suffered impairment of haemopoiesis, which in the more severely affected case persisted for two months after the last infusion of dextran. The authors thought this was due to the fact that the dextran is taken up by the reticuloendothelial system and therefore of the bone marrow and only slowly released and excreted or metabolized. The hepatic enlargement which occurred in two of their cases was presumably from this cause, although histochemical examination of the liver from one case at necropsy failed to reveal the presence of any dextran. Dextran is also deposited in the renal tubules.[5] Michie and Ragni[6] noted that the repeated intravenous administration of it significantly decreased the maximal tubular excretory capacity for *para*-aminohippurate in two out of five subjects with normal kidneys and in three out of four patients with pre-existing renal disease. The significance of this finding in such a small series of patients is doubtful, particularly in view of other evidence of the innocuousness of dextran where the kidneys are concerned.[1 7 8]

Most reports indicate that single infusions of dextran are not very effective in delivering nephrotic oedema,[1 2] and Mollison and Rennie's experience is no exception to this. There is little doubt that dextran is a powerful diuretic and may succeed when all other measures fail, but by the very nature of its route of administration and the transience of its effects it is unsuitable for use in domiciliary practice.

[1] Wallenius, G., *Scand. J. clin. Lab. Invest.*, 1950, **2**, 228.
[2] *Proc. Mayo Clin.*, 1953, **28**, 199.
[3] *J. Immunol.*, 1953, **70**, 514.
[4] *Reports to the National Research Council Subcommittee on Shock*, Jan.–April. 1952.
[5] Froeb, H. F., *et al.*, *Fed. Proc.*, 1952, **11**, 51.
[6] *J. appl. Physiol.*, 1953, **5**, 625.
[7] Raisz, L., *J. Lab. clin. Med.*, 1952, **40**, 880.
[8] Harrison, J. H., *Ann. Surg.*, 1954, **139**, 137.

PHOTIC CONVULSIONS

Cases have been reported from time to time of epileptic seizures apparently induced by flashing lights, such as sunlight through rows of trees. But it was Grey Walter and his associates[1] who first showed systematically that rhythmic visual stimulation produced widespread physiological effects, leading in some cases to clinical epileptic attacks. Since then several modifications of the original technique have been made, such as triggering the stimulus frequency by a "feed-back" circuit from frequencies present in the stimulated brain.[2] Gastaut[3 4] introduced the combination of injected metrazol with photic stimulation. Many studies of the effects of these methods of examination in various neurological and psychiatric conditions have now appeared. Recently Bickford, Daly, and Keith[5] have reported on 27 epileptic children who all showed, on photic stimulation, epileptic discharges in their electroencephalogram, often with clinical attacks as well. As found by other workers, the effective flash frequencies were usually between ten and twenty flashes per second, and myoclonic jerks were the commonest clinical manifestation. Arrest of speech and clinical petit mal sometimes occurred. In several cases there was a clinical history of minor attacks precipitated by light stimuli. One child sometimes induced attacks at will by waving his fingers in front of his eyes, apparently getting a pleasurable sensation thereby. The authors do not specifically discuss the aetiology of their patients' epilepsy, but several obviously have diffuse degenerative cerebral disorders, and others have so-called idiopathic epilepsy.

[1] Walter, W. G., *et al.*, *Nature, Lond.*, 1946, **158**, 540.
[2] Shipton, H. W., *J. Brit. I.R.E.*, 1949, **4**, 374.
[3] Gastaut, H., *Electroenceph. clin. Neurophysiol.*, 1950, **2**, 249.
[4] —— and Hunter, J., ibid., 1950, **2**, 263.
[5] Bickford, R. G., *et al.*, *Amer. J. Dis. Child.*, 1953, **88**, 170.
[6] Ulett, G. A., *Arch. Ophthal. (Chicago)*, 1953, **50**, 685.
[7] Williams, D., *Brain*, 1953, **76**, 50.
[8] Wall, P. D., *et al.*, *Electroenceph. clin. Neurophysiol.*, 1953, **5**, 385.

A rational treatment of this abnormal light sensitivity would seem to be to cut down the intensity of visual stimulation by dark glasses. Bickford and his colleagues noted that this was an effective adjuvant to drug therapy in some cases. Ulett[6] has used dark glasses to prevent laboratory staff exposed to experimental stimulation from suffering ill effects. Trimethadione and amylobarbital are the most effective drugs in diminishing photosensitivity, especially when given intravenously. No one seems to have followed up the odd fact that the former drug, the most effective of all, has the unpleasant side-effect of producing glare and other visual disturbances, contrary to what might have been expected.

Abnormal photosensitivity, leading to the production of epileptic discharges in the E.E.G. and even myoclonic jerks, occasionally occurs in subjects who have never had any spontaneous epileptic attacks of any sort. Some hysterics, schizophrenics, and children with behaviour problems, for example, will give myoclonic jerks with photic stimulation (and no metrazol). Anticonvulsants are usually beneficial only to patients with spontaneous epileptic attacks: rarely, for example, will a pure behaviour disorder occurring in a photosensitive child respond to anticonvulsants. As these authors remark, neither their clinical studies nor current neurophysiological research gave unequivocal evidence of the pathways responsible for the abnormal spread of impulses from the visual to the motor systems. Gastaut and Hunter's experiments[3] pointed to a subcortical, possibly thalamic "leak" (a view supported by Williams's observations[7] on thalamic activity in spontaneous petit mal), but recent studies[8] have indicated the pre-tectal region. The mechanism certainly appears different in pathway and function from the normal nonspecific arousal responses obtainable from the reticular substance of the central grey matter. The solution of this problem may shed light on many neuropsychiatric disorders apparently far beyond the borderlands of epilepsy.

DANGERS OF EFOCAINE

Last year Iason and Shaftel[1] described the use of a solution known as "efocaine" for producing long-lasting local analgesia in the neighbourhood of operation wounds. They obtained favourable results in 100 cases. Efocaine contains procaine as base 1%, procaine hydrochloride 0.25%, butyl-*p*-aminobenzoate 5%, in a solvent composed of 2% polyethylene glycol, 78% propylene glycol, and water. When injected near the incision they found that efocaine produced analgesia for a period which varied from six to eighteen days as determined by the response to pricking the skin. Iason and Shaftel state that "when efocaine is injected into the tissue, the contact with the body fluid causes a deposition of the active ingredients producing anaesthetic depot." To obtain by this means more or less complete absence of pain around the incision is a notable achievement, and there have been several papers from surgeons giving favourable accounts of the use of efocaine. It has been used to relieve the pain of fissure- and fistula-in-ano, to control the pain after removal of haemorrhoids, and to relieve pruritus ani; for caesarean section, episiotomy, and hysterectomy; for hernia, cholecystectomy, and gastrectomy. When it has been used it is stated that much less morphine, codeine, and pethidine have been required, but in many places these drugs are given as a postoperative routine, sometimes perhaps when not required. In this country Roualle[2] obtained a good result in eight and a fair result in three out of fourteen patients. He pointed out that to be effective the efocaine should be deposited close to the nerves supplying the area, and therefore he recommended a nerve block in preference to local infiltration.

More recently there have been accounts[3 4 5] of some disadvantages of efocaine. After its use there have been perirectal sloughs, unilateral anhidrosis, severe neuralgia persisting for weeks, neuritis, prolonged motor paralysis of the legs, and atonic bladders. Finally, Angerer, Su, and Head[6] have described a death which was clearly due to efocaine, when it was used to produce an intercostal nerve block. During the injection, when 1.5 ml. of efocaine had been given, the patient complained of severe pain in his back and radiating down both legs. He collapsed and died forty-four hours later. At necropsy there was acute thrombophlebitis of the 8th intercostal vein, and focal necrosis and acute inflammation of the spinal cord. The spinal fluid gave a positive test for procaine. The authors conclude that efocaine, "since it may produce myelitis and even death, should not be used for local anaesthesia, especially in a region near a vital organ such as the spinal cord."

The substances present in efocaine taken separately are not toxic, though butyl-*p*-aminobenzoate is a substance with a structure not wholly unlike that of butyn, which is a toxic anaesthetic. However, when present together in efocaine they may clearly damage both vascular and nervous tissue, with serious consequences in some patients, the changes being probably due to one or other of the solvents. Mannheimer and his colleagues[7] have recently reported that perineural injections of efocaine in animals caused coagulation necrosis of the nerve fibres, and that the propyleneglycol and polyethylene glycol mixture (solvent for efocaine) alone and mixed with 5% butyl-*p*-aminobenzoate caused muscle and nerve changes identical to the changes caused by efocaine. This evidence also prompts the inquiry how far it is good physiological practice to seek to produce prolonged local analgesia in the neighbourhood of a healing wound. Are there grounds for supposing that the impulses arising in the sensory nerves carry out no useful or important function? Certainly the deposition of a large amount of foreign matter cannot evoke the normal tissue reaction in an anaesthetized area, and it is not surprising to learn of untoward results following this practice.

[1] Iason, A. H., and Shaftel, H. E., *Amer. J. Surg.*, 1952, **83**, 549.
[2] Roualle, H. L. M., *British Medical Journal*, 1952, **2**, 1293.
[3] Bonica, J. J., *J. Amer. med. Ass.*, 1952, **150**, 1581.
[4] Shapiro, S. K., and Norman, D. D., ibid., 1953, **152**, 608.
[5] Sullivan, M. B., and Gerber, M. L., *U.S. armed Forces med. J.*, 1954, **5**, 100.
[6] Angerer, A. L., Su, H. H., and Head, J. R., ibid., 1953, **153**, 550.
[7] *J. Amer. med. Ass.*, 1954, **154**, 29.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

LIVER-FUNCTION TESTS

BY

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In view of the very large number of liver-function tests which have been elaborated, the present discussion is limited to a few tests of established value. These tests can be divided into two groups according to the nature of the material required. Tests in the first group can be performed on material collected by the practitioner, whereas those in the second group require the attendance of the patient at a laboratory or hospital centre or, alternatively, a personal visit by the pathologist. Tests performed on material submitted by the practitioner include serum bilirubin, serum alkaline phosphatase, flocculation tests, serum albumin and globulin estimations, and qualitative urine tests for bile pigments. More elaborate tests are the quantitative estimation of urine bile pigments, bromsulphthalein retention, and prothrombin response to vitamin K.

The blood tests in the first group require the collection of approximately 10 ml. of clotted blood reasonably free from haemolysis. To achieve this it is necessary to use a dry sterilized syringe and to remove the needle before squirting the blood gently into the dry collection tube. Urine can be naturally voided and should preferably be an afternoon specimen, since the amount of urobilinogen, for example, is small in morning specimens. It is, in general, inadvisable to rely upon any one test of liver function, and a "battery" of tests is usually employed. This need not necessarily include all the tests mentioned, and some guidance on the choice of tests is given below.

The various tests are considered individually in relation to their usefulness in the diagnosis of liver diseases.

Serum Bilirubin

It is difficult to avoid discussion of technique in this test, as so many different methods have been used since the pioneer work of van den Bergh. I prefer a separate estimation of "direct" and "indirect" serum bilirubin by a photoelectric method based on that of Malloy and Evelyn. With this technique direct pigment refers to colour developed in aqueous solution after 15 minutes, while the total pigment is read in alcoholic solution at 30 minutes. The indirect pigment represents the difference between the two values. Terms such as direct, indirect, and biphasic reaction are also used, but they are difficult to define quantitatively.

The normal total serum bilirubin is from 0 to 1 mg. per 100 ml. of serum, and a zone of latent jaundice not clinically detectable exists between 1 to 3 mg. per 100 ml., patients with values over 3 mg. being usually clinically jaundiced. The demonstration of latent jaundice is an important aid to diagnosis in conditions such as infective hepatitis, hepatic cirrhosis, and the haemolytic anaemias. In jaundiced patients both the direct and the indirect bilirubin will increase, but if more than half the total is indirect the jaundice is probably haemolytic in nature. Jaundice due mainly to increase in direct pigment is usually either obstructive or toxic and infective.

The serum bilirubin estimation is an important basic procedure as it provides an accurate record of the intensity of any jaundice which may be present. It may nevertheless give normal results in certain cases of chronic liver disease such as cirrhosis, carcinomatosis, etc.

Serum Alkaline Phosphatase

The serum alkaline phosphatase is an enzyme produced mainly in the bones by the osteoblasts but also by the liver cells. It can therefore only be used as a liver-function test in cases in which the bones can be assumed to be normal. Its level in the blood (normal 3 to 13 King–Armstrong units) is elevated in a variety of liver conditions such as obstructive jaundice, hepatitis, carcinomatosis, abscess, amyloidosis, and cirrhosis. It is, however, on the whole much higher in obstructive jaundice than in the other conditions named, and values over 35 units, for example, are particularly suggestive of obstruction as opposed to hepatitis in a jaundiced patient. In the differential diagnosis of jaundice it is particularly valuable to combine this test with one or more of the flocculation tests.

Flocculation Tests

Under this heading are included a rather large number of empirical procedures which have been used to demonstrate hepatic dysfunction, ranging from the earlier formol-gel and Takata–Ara reactions to more recent tests such as the serum colloidal gold reaction and the thymol turbidity and flocculation tests. There are, however, considerable individual differences in these various tests, and the following remarks apply mainly to the thymol and gold tests.

These tests are positive, particularly in acute infective hepatitis (about 90%) and in cirrhosis (about 50%), and have a special tendency to be negative in obstructive jaundice. They are therefore of value in the detection of hepatitis and in the differential diagnosis of jaundice. It should always be remembered that they are not specific tests of liver damage, as they depend upon a particular type of serum protein disturbance which may also occur in various acute and chronic infections such as glandular fever, malaria, infective endocarditis, etc. The necessity of interpreting all laboratory procedures with due regard to the whole clinical picture applies particularly to these tests.

Serum Albumin and Globulin Estimations

These tests are of most value in the more chronic types of liver disease such as cirrhosis. In cirrhosis the albumin (normal 4 to 5.5 g. per 100 ml.) tends to fall and the globulin (normal 1.5 to 3 g. per 100 ml.) to rise. Alternatively, one may say that the albumin/globulin ratio (A/G ratio) (normally about 2:1) tends to fall in liver disease, but as changes in the two fractions are largely independent of one another it is preferable to consider the values individually. Neither change is an entirely specific indication of liver damage, but if both alterations are present hepatic disease is the most likely explanation.

These tests are of value in confirming a diagnosis of cirrhosis. From the prognostic point of view the albumin is the more important estimation, values below 2 g. per 100 ml. indicating a poor prognosis, and usually being associated with an obstinate oedema. High globulin values, on the other hand, are compatible with good health and do not usually produce symptoms. These estimations, based on

salting-out procedures, are to some extent becoming replaced by electrophoretic analysis of the serum proteins. However, this procedure is not available in all laboratory centres and rules for the interpretation of results are not yet so firmly established.

Qualitative Urine Tests for Bile

The ordinary clinical tests for bile such as the foam and iodine tests are, of course, very insensitive. The following remarks refer to tests such as the Harrison–Fouchet test for bilirubin and the Ehrlich–Watson test for urobilinogen. These tests reach their maximum usefulness in patients who are not clinically jaundiced. In such cases the occurrence of bilirubinuria suggests a latent jaundice usually due to hepatitis or to biliary obstruction, and this test may be positive some days before a rise in the serum bilirubin can be demonstrated. The test is therefore particularly valuable in the pre-icteric phase of infective hepatitis and in hepatic cirrhosis.

An increase in urine urobilinogen may accompany bilirubinuria but may also occur without any latent jaundice in chronic liver damage such as hepatic cirrhosis. It is a less specific indication of liver pathology than bilirubinuria and may occur as a temporary event in febrile states. Urobilinuria may also occur in jaundiced patients but is of limited diagnostic value in this group; on the whole, increased values are suggestive of toxic and infective jaundice, but there are many exceptions to this rule.

Quantitative Estimation of Urine Bile Pigments

As noted above, the urinary excretion of urobilinogen is increased as a result of liver damage, and this increase is best demonstrated by a quantitative estimation. Urobilinogen is formed mainly by the bacterial decomposition of bilirubin in the intestinal tract. It is partially reabsorbed from there into the blood stream and is partly re-excreted by the liver in the bile. It follows from this that urine for this test should not be collected in the morning, when the effects of bile flow will be minimal, and also that the investigation is of greatest value in patients not clinically jaundiced. In the absence of jaundice it can be assumed that bile is reaching the intestine, whereas in the presence of jaundice this may not be the case.

Although this examination can be carried out on 24-hour urine specimens it is more convenient to collect a timed specimen of urine in the afternoon and to estimate the amount of pigment in a one- or two-hour specimen by the methods of Watson. Normal values for urobilinogen are from 0 to 1 Ehrlich unit per 2 hours or up to 3 mg. per 24 hours.

The interpretation of this estimation is very similar to that given for the qualitative urobilinogen test above, but the procedure is more accurate and reliable. The test is of particular value in non-jaundiced cases of hepatitis and cirrhosis.

Bromsulphthalein Retention

Bromsulphthalein (phenoltetrabromphthalein disodium sulphonate) is a harmless dye which is injected intravenously and is excreted mainly in the bile. The recommended dosage is 5 mg. per kg. body weight and blood is collected exactly 45 minutes after injection. The amount of bromsulphthalein remaining in the serum is estimated. Normal subjects will show no significant bromsulphthalein retention at 45 minutes, and in pathological states the amount remaining in the circulation at this time is expressed as a percentage of the injected dose to give a figure of percentage bromsulphthalein retention.

Like the preceding test this is of little value in jaundiced subjects and is mainly used in non-jaundiced subjects and in cases of hepatitis and cirrhosis. It is a sensitive and convenient test in cases of this type, although even this test is not invariably positive in cirrhosis. It will also indicate the existence of liver dysfunction in other conditions, such as malaria, diabetes mellitus, glandular fever, etc.

Prothrombin Response to Vitamin K

This test has been used mainly in cases of obstructive jaundice but is also of value in the differentiation between surgical and non-surgical jaundice. It is, of course, applicable only to those patients who have low prothrombin values when first seen. This may happen either because the exclusion of the bile from the intestine interferes with the absorption of vitamin K (obstructive jaundice) or because the liver is too severely damaged to manufacture vitamin K from its plasma precursors (hepatitis or cirrhosis). About a quarter of all jaundiced subjects may be expected to exhibit an initial deficiency in prothrombin and therefore become eligible for this test.

After the initial estimation vitamin K is administered, usually as 50–100 mg. of a water-soluble preparation, and the prothrombin is again estimated after 24 to 48 hours. A rapid return towards normal indicates good liver function and confirms the diagnosis of biliary obstruction. An absence of response indicates gross liver damage and suggests a hepatogenous origin for the jaundice. In practice the first part of this test is often omitted; a low prothrombin value after adequate vitamin-K therapy is, of course, significant even in the absence of the preliminary observation.

Quite apart from its value in diagnosis the test is of great importance if operation is contemplated, as a low plasma prothrombin value indicates a greatly increased risk of haemorrhage.

Combination of Tests

Certain tests are particularly suitable for use in combination, and this applies especially to the serum alkaline phosphatase estimation and the thymol flocculation test in relation to the differential diagnosis of jaundice. The individual variations in these two tests have already been discussed, but the accuracy of diagnosis is improved when they are undertaken simultaneously. Thus cases of jaundice with negative thymol tests and serum alkaline phosphatase values above 35 units are almost invariably obstructive in nature, whereas those with strongly positive flocculation tests and/or with normal serum alkaline phosphatase levels are usually non-obstructive. In some 20% of cases the findings fall between these two extremes and are of no diagnostic value.

Indications for Liver-function Tests

Laboratory procedures in general can only be used to answer certain restricted types of question, and it is important to have a clear idea of exactly what the provisional diagnosis is before any help can be expected from tests of this type. Most of the indications for the tests will fall under one or more of the following heads:

In suspected primary liver disease the condition may be either acute or chronic in nature—for example, infective hepatitis or hepatic cirrhosis. Any of the tests described may assist in making the diagnosis, their relative importance varying, however, with the type of case. In pre-icteric hepatitis the first tests to become positive are those for urine bile pigments, particularly bilirubin. At a later stage all the pigmentary tests will be positive and usually the flocculation tests in addition. In hepatic cirrhosis, on the other hand, the pigmentary tests and many of the others may be at times completely negative and more reliance is placed upon the serum protein estimations and the bromsulphthalein retention.

The liver may be secondarily involved in a variety of diseases. In heart failure, for example, the turbidity and flocculation tests are often positive and urobilinuria may occur. In malaria and glandular fever the positive flocculation tests constitute the most frequent abnormality, while in thyrotoxicosis the disturbance is of a different type and may require the use of tests such as a galactose-tolerance test and a hippuric-acid test, which are not especially valuable for general diagnostic purposes.

The differential diagnosis of hepatic enlargement tends to be concerned mainly with the problem of distinguishing hepatic cirrhosis from carcinomatosis. The biochemical changes are usually distinctly different in the two groups, the serum protein and flocculation tests being mainly altered in cirrhosis while the raised serum alkaline phosphatase is the main change in carcinomatosis.

In the differential diagnosis of jaundice we are usually trying to distinguish jaundice due to a mechanical obstruction of the bile passages from that due to hepatitis or cirrhosis. As noted above, the thymol flocculation test and serum alkaline phosphatase used in combination give the best results in cases of this type, making the distinction satisfactorily in about 80% of such cases, the results being equivocal in the remaining 20%. Some assistance can also be given in the detection of haemolytic jaundice in which the indirect serum bilirubin is more raised than the direct pigment, and the serum alkaline phosphatase tends to be normal.

The tests principally used in the *prognosis of liver diseases* are the serum albumin estimation and the prothrombin response to vitamin K. In cirrhosis values for the serum albumin below 2 g. per 100 ml. indicate an irrecoverable liver damage with a poor prognosis. In obstructive jaundice failure of a low prothrombin level to respond to vitamin-K therapy suggests grave liver damage and a poor operative risk.

The investigation of anaemias is, of course, the province of the haematologist, but the differential serum bilirubin estimation may assist in the detection of haemolysis, in which the indirect pigment is mainly increased. This finding has been found valuable in the diagnosis not only of the various haemolytic anaemias but also in cases of pernicious anaemia.

Choice of Test

As mentioned above, it is usually desirable to combine several different tests, and the following scheme may be taken as a guide.

Tests for Routine Application.—Serum bilirubin, serum alkaline phosphatase, flocculation tests, qualitative urine tests for bilirubin and urobilinogen: this small battery of tests will often give all the information required, at all events from a diagnostic standpoint. They will establish the absence or presence of jaundice, and if jaundice is present they will provide a record of its intensity and will also give a good indication of its probable cause. In the non-jaundiced patient, on the other hand, one or more of the tests may be positive and provide enough evidence to confirm a suggested diagnosis of hepatic disease.

Further Tests.—If the above tests are negative or if their indications are in any way equivocal the remaining tests mentioned may be undertaken in the following order of preference: serum albumin and globulin estimations, quantitative estimation of urine bile pigments, bromsulphthalein retention, prothrombin response to vitamin K. It will usually be unnecessary to do more than one or two of these additional tests in order to support, for example, a diagnosis of liver cirrhosis, but the vitamin-K test is specifically indicated in surgical jaundice.

Conclusion

In conclusion it may be emphasized that modern liver-function tests reach a high degree of sensitivity and will rarely fail to demonstrate any significant liver damage which may be present. This implies that the disturbances of function occurring in various non-hepatic diseases may complicate interpretation, which should always be undertaken with due regard to the whole clinical picture.

Next article on Clinical Pathology.—"Laboratory Investigations in Suspected Industrial Poisoning," by Professor R. E. Lane.

Reports of Societies

CONVULSIONS IN CHILDHOOD

The Section of Paediatrics of the Royal Society of Medicine met under the chairmanship of Dr. C. T. Potter on March 26 to discuss "The Significance of Convulsions in Infancy and Childhood."

Dr. PETER TIZARD (Paediatric Unit, St. Mary's Hospital, Paddington) opened with a general review of the aetiology of convulsions. Most textbooks divided fits into the symptomatic—those caused by fever, cerebral tumour, brain injury, etc.—and the idiopathic, which included infantile convulsions, pyknolepsy, and true epilepsy. Was this sort of division justifiable? With regard to symptomatic convulsions, we did not know the effective cause, in the Aristotelian sense, of any fit. Clearly fever, for example, in itself could not be regarded as a cause. Were it so any individual would have a fit whenever his temperature reached a certain critical height, whereas in fact that happened only with an extremely small minority of children. Similarly, a focal lesion, such as a cerebral tumour or brain injury, could not in itself be the cause of a fit; if it were, the patient would convulse continuously and not intermittently.

Probably, in the production of any one fit there were several causative factors. This view led to the concept of a "convulsive threshold," to the idea that there was no fundamental difference between the epileptic and the non-epileptic, and that any person given an adequate stimulus would have a fit. The nature and degree of stimulus would vary widely, of course; at one end of the scale were those who would convulse only in response to a severe electric shock or an injection of insulin, while at the other end the threshold was so low that fits seemed to occur spontaneously. Between these two extremes were those who developed fits in response to such precipitating factors as fever or brain injury.

This view, that we are all potential epileptics but have varying degrees of natural resistance, provided a useful method of approach to the parent of a child who had fits. It took away much of the sting that goes with a diagnosis of epilepsy. Useful though it was, however, it represented an over-simplification of the problem. There was no evidence of hereditary predisposition in some forms of symptomatic epilepsy. In conclusion, Dr. Tizard discussed the possibility that included in what we now call idiopathic epilepsy there were several different diseases of unknown aetiology and pathology, of which the main symptom was the occurrence of fits.

The First Fit

Dr. CHRISTOPHER OUNSTED (Research Assistant to the Oxford Regional Hospital Board) spoke about the "First Fit." Its significance in a young child depended on the setting in which it occurred. In severe infections multiple fits were common and were of grave prognostic significance. Prolonged fits and status epilepticus were fatal *per se*. Dr. Ounsted gave figures showing that a sharp reduction in the mortality of purulent meningitis, and a parallel reduction in the incidence of fits, could be achieved by giving prophylactic anticonvulsants to affected children. Established convulsions should be aborted as rapidly as possible; phenobarbitone and chloral were valueless once a fit had begun, but sodium amylobarbitone given intramuscularly in doses from 0.125 to 0.25 g. controlled convulsions rapidly and safely.

After a single fit the regular use of anticonvulsants was not necessary, but the child should be given prophylactic phenobarbitone during any future febrile illness up to the age of 4 years. This measure seemed to be effective in preventing fits, and the mothers were comforted by having some practical steps offered to them.

The relationship between infantile convulsions and adult epilepsy was not known, and studies made by different workers had given conflicting results. The paediatrician's problem was to give a prognosis at the time of the first fit. Various prognostic criteria had been proposed; in particular much weight had been given to electro-encephalographic abnormalities and to a family history of epilepsy. Neither of these criteria was a reliable guide. Study of 800 family trees of children with convulsive disorders had shown that benign convulsions and intractable epilepsies were often found in the same family. The E.E.G. was not a prognostic instrument in childhood. Records made on young children were often inscrutable.

E.E.G. Studies

Dr. W. A. COBB (Department of Applied Electrophysiology, National Hospital, Queen Square) gave an account of the contribution of electro-encephalography to the study of fits. The characteristic 3-cycle per second spike-and-wave tracing of petit mal remained a problem. Though it was always present, he thought, in petit mal, it might also occur in subjects with other types of fit, or rarely in subjects who were not suffering from any form of fit. Several tracings were shown in which, in addition to the usual spike-and-wave episodes, there was an occipital delta rhythm with bilateral foci in the occipito-temporal regions. Evidence was accumulating to suggest that this combination might provide a means of recognizing a certain type of epilepsy in children, a type hard to treat successfully but with nevertheless an excellent ultimate prognosis. The existence of such a group of cases with electro-encephalographic diagnostic criteria might perhaps justify a revival of the old term of pyknolepsy.

Post-mortem Appearances

Dr. L. CROME (Fountain Hospital) gave an account (illustrated by slides) of the morbid anatomical findings in a series of 61 epileptics from an institution devoted to low-grade defectives. Gross structural abnormalities, affecting chiefly the cerbral cortex, were found in all these cases, and his material afforded no support for the existence of idiopathic epilepsy.

It was difficult to be sure to what extent comparison was justifiable with normally intelligent patients with fits, but it seemed possible that processes in the group with severely deranged brains were often greatly magnified reproductions of similar events occurring in more normal individuals.

Discussion

Dr. T. STAPLETON wondered whether there might not be some danger of adding to anoxia if phenobarbitone were given as a routine in cases of bronchopneumonia in small children. Dr. OUNSTED replied that he felt sure that there was no danger of this in the small dosage used.

Dr. R. M. MAYON-WHITE asked to what extent intrathecal therapy was related to the incidence of fits in purulent meningitis, and Dr. OUNSTED said that no correlation had been observed at Oxford.

Dr. E. S. STERN mentioned that Dr. Gillman had shown that barbiturate poisoning could be successfully treated with picrotoxin even in advanced cases, and that 1 g. of sodium hexobarbitone intramuscularly was an effective treatment for status epilepticus in adults.

Dr. HUGH ELLIS and others, including the CHAIRMAN and Dr. OUNSTED, commented on a pamphlet* recently issued by the Ministry of Health in which it was suggested that cases of fits should be notified to the school medical officer as soon as possible after the age of 2 years. It was generally agreed that this would be most inadvisable, as one or more convulsions at this age might have no prognostic significance whatever.

*Ministry of Health Circular No. 26/53, December, 1953—Welfare of Handicapped Persons. The Special Welfare Needs of Epileptics and Spastics.

There was little time for discussion after the four opening papers, which, as is usually the case, considerably exceeded their allotted time. This was a pity, especially as the subject of the meeting was of general medical interest. There might be something to be said for a compromise between this sort of meeting, which, valuable as it may be, is certainly not a discussion, and the sort of channelled and controlled—and sometimes artificial—discussion with which the B.B.C. has made us familiar.

LOCAL MEDICAL SOCIETIES

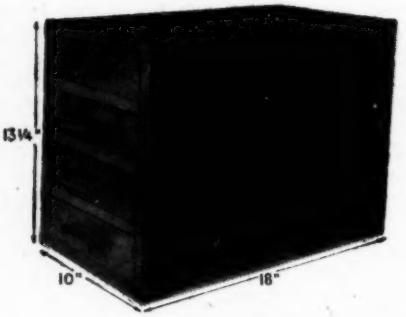
Liverpool Medical Institution

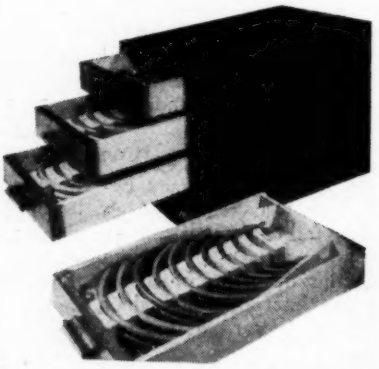
Speaking at a meeting on March 18, Sir Reginald Watson-Jones stressed the need for a clearer conception of what constituted a minor injury. Many finger injuries, hitherto regarded as minor, were in fact major and responsible for men being off work for long periods at a time. A simple strained ankle might turn out to have a recurrent subluxation associated with a displaced astragalus, and a badly handled shoulder dislocation might be the start of a recurrent dislocation. On the other hand, fracture-dislocation of the pelvis, commonly regarded as a major injury, usually gave rise to little trouble if properly managed. At the beginning of the meeting Dr. Henry G. Carlisle and Dr. G. F. Rawdon Smith were admitted, with acclamation, to life membership of the institution.

Preparations and Appliances

STORAGE CABINET FOR ENDOTRACHEAL TUBES

Dr. M. J. HARKER, consultant anaesthetist, Shrewsbury Group Hospital Management Committee, writes: I find the cabinet illustrated a very useful and time-saving adjunct to the anaesthetic department. It was devised by the theatre sister (Sister K. Wilks) and made by the carpenter (Mr. W. H. Edwards) at Copthorne Hospital, Shrewsbury. It is simple in construction, it facilitates the instant selection of any size or type of tube, and the tubes are kept at their correct curve by the kidney-shaped blocks. The cabinet fits conveniently under the ordinary dressing trolley, such as is used for the intravenous tray in the anaesthetic room. The top drawer, 8⅞ by 2½ in. (22.5 by 6.4 cm.), has a division in the centre and is used for airways and connexions. The second, third, and fourth drawers, of the same dimensions, have central kidney-shaped blocks ¾ by 1½ by 2½ in. (1.9 by 3.8 by 6.4 cm.). There are two side pieces 8½ in. (21.6 cm.) long, to narrow the width of the drawer for the smaller tubes. The second drawer houses cuffed tubes, the third drawer nasal tubes, and the bottom drawer oral tubes.





Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Action of Chlorpromazine and Promethazine

SIR,—On April 2 a discussion took place at the Royal Society of Medicine on the action of chlorpromazine and promethazine. In practical anaesthesia these two substances are used together with pethidine. In the discussion it became clear that anaesthetists are not much interested in the fall of temperature which chlorpromazine produces, and that these substances are used together for their peculiar anaesthetic action.

Since from the pharmacological evidence there is not very much to choose between these substances so far as their central action is concerned, would it not be possible for observations to be made in patients using only one substance at a time? It would be of great value to know whether a dose of 200 mg. chlorpromazine given alone would have different effects from 200 mg. promethazine given alone, or from 200 mg. pethidine given alone. It would be important that the observations on the effect of these substances should be made by somebody who did not know which of the compounds had been administered, in order to exclude preconceptions in making the comparison.—I am, etc.,

Oxford. J. H. BURN.

Hibernation Anaesthesia

SIR,—Drs. Angus Smith and J. G. Fairer (*Journal*, March 27, p. 759) suggest that the case of "prolonged hypotension following hibernation anaesthesia" described by us (*Journal*, March 13, p. 645) was in fact due to surgical shock, the result of inadequate anaesthesia. In reply we would like to make the following points.

(1) The patient was a small—120 lb. (54.4 kg.)—frail, elderly woman. In accordance with usual pharmacological practice we considered that a reduction in dosage, in relation to age and body weight, was indicated. (2) The dosage of the "potentiating mixture" given (chlorpromazine 12½ mg., promethazine 12½ mg., pethidine 25 mg.) produced the usual picture obtained after its exhibition in the doses recommended by Smith and Fairer[1]—loss of consciousness, slight hypotension, initial rise in pulse rate, lack of response to painful stimuli, ease of intubation without muscle relaxants. (3) At no time during the operation were there any signs of inadequate anaesthesia. The blood pressure levelled off at 80/45 mm. Hg; the pulse rate remained steady at 120/minute (pre-operative level 100/minute); there were no voluntary movements, no sweating, and no lacrimation. The "aliquot mixture of nitrous oxide and oxygen" would appear to have been sufficient for adequate anaesthesia, its effect presumably being potentiated by the "lytic cocktail." The indications for supplementary doses of "lytic cocktail" are a rise in pulse rate and/or blood pressure,[1] neither of which occurred during the operation on our case. (4) Our "hibernation anaesthetic" cases hitherto had awakened some 4–5 hours after the start of the hibernation, by which time the blood pressure was nearly at pre-operative levels. After the elapse of nearly four hours the case reported was still deeply unconscious and not reacting to deep painful stimulation. The usual picture of post-operative shock was absent (hypotension, hypothermia, clammy skin, cyanotic lips and nail-beds, rise in pulse rate, intense peripheral vasoconstriction). Although there was profound hypotension (50/20 mm. Hg) and hypothermia, the skin was quite dry. the lips and nail-beds were pink, the pulse rate was still 120/minute. We also feel that inadequate anaesthesia would have been accompanied by evidence of returning consciousness. (5) Chlorpromazine, according to Courvoisier *et al.*,[2] diminishes, abolishes, or reverses the hypertensive effects of an intravenous injection of adrenaline, but in the same doses and conditions only diminishes the hypertensive effects of *nor*adrenaline and even in high doses does not reverse the hypertensive effects of *nor*adrenaline. (In view of our experience with this case under discussion, one of us has given 0.05 mg. *nor*adrenaline intravenously to a patient whose blood pressure was 70/40 mm. Hg (170/90 mm. Hg pre-operatively) 40 minutes after the exhibition of a mixture containing chlorpromazine 50 mg., promethazine 50 mg., pethidine 100 mg. The blood pressure was raised immediately to 130/70 mm. Hg.)

We feel satisfied that the case under discussion was not suffering from traumatic shock, but appeared to be suffering from a continuing effect of the modified dose of the "lytic cocktail." Although similar results have not occurred in our other cases and have not been reported elsewhere, we felt justified in describing our experience and the method used to produce a favourable outcome.—We are, etc.,

HUGH Y. WISHART.
Glasgow, W.1. FRANK S. PRESTON.

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2 *Arch. Int. Pharmacodyn.*, 1953, **92**, 305.

Carbon Dioxide Retention Simulating Curarization

SIR,—In your issue of March 6 (p. 565) Dr. C. V. Scurr recorded a case of "Carbon Dioxide Retention Simulating Curarization." In the *Journal* of April 3 (p. 820) Drs. T. C. Gray and E. S. N. Fenton report on a similar condition in one of their patients. To my mind, however, there is very little similarity between the two, and I do not think that the latter can be considered as offering confirmatory evidence of CO_2 retention as such.

In the case cited by Dr. Scurr, no periods of anoxia were recorded, and post-operatively "it was noted that such respiratory effort as was present was not marked by any urgency, neither was it accompanied by any tracheal tug, both of which features are usually present in cases of residual curarization." In Drs. Gray and Fenton's case, on the other hand, several periods of anoxia were admittedly experienced by the patient on each occasion, particularly on the second. Due to the pre-operative cardiac condition, it is more than likely that this anoxia was tolerated very poorly. At the conclusion of the second operation, "in view of the increasing cyanosis and distress, and loss of consciousness, an endotracheal tube was introduced." Surely this was gross anoxia. They then go on to state that the striking features of the patient on this occasion were "(1) inadequacy of the tidal exchange compared with the forceful chest movements and tracheal tug . . . , and (2) the bounding forceful pulse." Dr. Scurr attributes the features in (1) above to residual curarization, and not to CO_2 retention.

In view of the evidence, I venture to suggest that on both occasions Drs. Gray and Fenton's patient was suffering from the combined effects of O_2 lack and CO_2 excess—in other words, asphyxia. It is also very probable that there was some degree of residual curarization.—I am, etc.,

Beckenham. P. M. F. MCGARRY.

Failed Forceps

SIR,—I was very interested to read Dr. R. Lisle Gadd's article on failed forceps (*Journal*, March 27, p. 735), which is a valuable contribution to the literature on one of the most serious complications that can befall a woman in labour. His article concludes that incomplete dilatation of the cervix (39%) is the main cause for failure, whereas in the Birmingham series occipito-posterior positions and deep transverse arrest of the head accounted for 56% of cases and incomplete dilatation of the cervix 20%.[1] Malposition of the foetal head was also 2½ times more common than undilated cervix in the Norwich series,[2] which has not been referred to by Dr. Gadd.

In the Manchester series only six out of 39 cases classified as incomplete cervical dilatation subsequently had a normal delivery, and only a further six had a low forceps delivery. This suggests that malposition of the foetal head, or some mechanical factor other than the failure of the cervix to dilate, was the main reason why the forceps failed. In Dr. Gadd's series incomplete cervical dilatation with occipito-posterior positions has been classified under the former category, whereas in my series and Mr. Law's we would have classified some of these cases under occipito-posterior positions or deep transverse arrest.

I have observed that in some cases of occipito-posterior position the anterior lip of the cervix becomes trapped between the head and the symphysis pubis, with the result that this cervical rim becomes oedematous and will never fully disappear unless the head is disimpacted and the cervix pushed up. This cervical lip, however, is no bar to a forceps delivery, provided manual rotation to occipito-anterior has been accomplished, and it is the malposition of the foetal head rather than the cervix that has led to the failed forceps.—I am, etc.,

Crewe. DEREK FREETH.

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[2] Law, R. G. (1953). Ibid., 2, 955.

Anaesthesia in Hospital Breech Delivery

SIR,—In his letter on the above subject (*Journal*, March 27, p. 758) Dr. D. C. Druitt asks for the reasons for advocating the use of the forceps on the aftercoming head. These reasons were very well stated by Baxter[1] a few years ago. In brief, his conclusions were that the maximum safe limit of traction on the shoulders is considerably less than the expulsive force of the uterus, so that, "when the patient is unable to expel the head by a spontaneous effort of normal magnitude, shoulder traction is unlikely to deliver a live infant." On the other hand, when forceps are used a very much greater traction is possible without any risk to the baby, provided that they are accurately applied to the sides of the aftercoming head. These views are based on good clinical and experimental evidence. There is also the less well-founded view that the blades of the forceps act as splints to the foetal head, and prevent dangerous fluctuations in shape and pressure at the moment of delivery.

The use of forceps on the aftercoming head is one of Smellie's greatest contributions to the art of obstetrics. His name is often erroneously associated with Mauriceau's technique of jaw flexion and shoulder traction, which was also the method used in this country by Giffard as early as 1725.[2] It is interesting to see how Smellie's teaching is receiving due recognition now after the lapse of two centuries, during which it was generally neglected.—I am, etc.,

Wivenhoe, Essex. WALTER RADCLIFFE.

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[1] *J. Obstet. Gynaec. Brit. Emp.*, 1949, 56, 95.
[2] Wendell-Smith, C. P. (1950). *St. Bart's Hospital J.*, 54, 59.

Considered Contraception

SIR,—May I be allowed to support Professor H. C. McLaren's letter on this subject (*Journal*, April 3, p. 817)? I would say that it is almost never justifiable to tell a patient that she must not have another pregnancy, and it should be done only when the adverse factor is permanent. In these circumstances it is my practice to offer bilateral partial salpingectomy as an alternative to contraceptive advice. The risk of abdominal operation is not unduly great.

As Professor McLaren says, the banning of further pregnancy to a young woman is a most serious matter, and advice on the subject should never be lightly given. Not only must her physical state be considered, but also her psyche. A woman who longs for children is often better undertaking a pregnancy at some extra risk rather than being condemned to perpetual sterility.—I am, etc.,

Leeds, 2. ANDREW M. CLAYE.

Appointment with Fear

SIR,—Half the patients I have ever treated smoke like chimneys. Whatever else happens to them, they don't die of cancer of the mouth. What are we coming to? We mustn't smoke for fear of getting respiratory cancer of some sort. The stuff we inhale makes breathing a dangerous procedure. The poisons we consume in our food are sure to kill us soon, and of course we may even die in our sleep. In addition, the mental state induced by these hazards is sure to hasten the inevitable attack of coronary thrombosis or peptic ulcer. It seems that the way of living to a reasonable old age is to become a High Court judge, diet rigidly, give up smoking, and move to a rural area (there would also be less chance of getting run over on a farm).

Isn't it about time that we gave both our patients and ourselves a proper sense of proportion before we develop into a nation of anxious hypochondriacs? We haven't yet caught up on our American friends (if their magazine advertisements are anything to go by), but we'd better do something about it soon. Let us help our patients to live—and die—without the dread picture of disease for ever in their thoughts; and let us refrain from giving the lay press so much ammunition to use in their quasi-medical fear-stimulating extracts. Finally, the only case of cancer of the mouth I have treated in 16 years of medical practice was in an old lady with no bad habits. She didn't even smoke.—I am, etc.,

London, E.9. PAUL R. SAVILLE.

Abdominal Testicles and Fertility

SIR,—The gonadotrophic hormone in small boys causes precocious secondary sexual changes. Since the day 25 years ago when I was first shocked by the sight of a group of youngsters receiving this (as I think) unfortunate form of treatment, I have taught that it is unjustifiable except in the case of gross hypopituitarism—a subject for the endocrinologist.

This is only the expression of an opinion, but I agree with Dr. Nicholas S. Craig (*Journal*, March 20, p. 706), Denis Browne, Great Ormond Street, and the Boston Children's Hospital, or, if Dr. G. I. M. Swyer (*Journal*, April 3, p. 815) prefers it so, they agree with me. My reason for writing is to draw attention to the serious physical and psychological side effects apart from which the suggested and too often practised therapeutic test might be attractive.—I am, etc.,

Liverpool, 7. CHARLES WELLS.

Fructose in Diabetes Mellitus

SIR,—In the *Journal* of February 27 (p. 510) you have published an annotation on "Fructose in Diabetes Mellitus." Since some of its implications might be misunderstood and lead to unnecessary and indeed dangerous experimentation, I would beg your permission to comment.

The annotation, as well as some of the original publications cited, clearly imply that most tissues of normal and diabetic animals can and do utilize significant amounts of fructose. By "utilize" I mean "metabolize in such a way as to derive some useful energy from it." It is, however, quite likely that in the mammalian organism, and in the presence of even small amounts of glucose, fructose is utilized almost exclusively by the liver and, to a lesser degree, by intestinal mucosa. Thus Bollman and Mann[1] have shown in 1931 that in the hepatectomized, eviscerated dog the intravenous administration of fructose results in little fructose disappearance, no slowing in the rate at which blood glucose decreases after hepatectomy, no slowing in the rate at which muscle glycogen decreases after hepatectomy, and no relief of hypoglycaemic convulsions. Gemmill[2] showed in 1941 that rat diaphragm cannot deposit glycogen when incubated with fructose, with or without the addition of insulin. This earlier evidence for lack of peripheral

fructose utilization has been recently confirmed conclusively by Wick and collaborators[3] using fructose labelled with C^{14} in eviscerated rabbits.

The concept of fructose utilization by skeletal muscle has been fostered by the demonstration of muscle enzymes capable of phosphorylating and further metabolizing fructose.[4] However, the primary product of fructose phosphorylation in both liver and muscle has been shown to be fructose-1-phosphate[5 6 7 8]—that is, a metabolite which is not a regular by-product or intermediate of glycolysis. The further metabolism of fructose-1-phosphate has been shown to differ in liver and in muscle,[5 6 7 9 10] and it might well be that in the intact muscle cell fructose-1-phosphate represents a metabolic dead end.

The presence of a normal fructose tolerance in the diabetic organism simply means that diabetic tissues utilize fructose as well (or as poorly) as normal tissues. Since in the normal neither brain cells nor muscle cells utilize a physiologically significant amount of fructose, there is no reason to believe that fructose utilization will be better in brain or muscle of the diabetic organism.

The statement that "fructose may prove to be a more useful sugar in conditions where glucose has a time-honoured place—for example, in the treatment of hypoglycaemia"—should be retracted. Hypoglycaemic convulsions occurred in the animals of Bullman and Mann as soon as blood glucose sank below the critical level, even though high blood fructose concentrations were maintained. It should be particularly kept in mind that most laboratory determinations of blood glucose also measure fructose, and that the danger of severe hypoglycaemia in the presence of what appears to be a normal or elevated "blood glucose"—that is, reducing sugar—determination is indeed a real one. The treatment of hypoglycaemia remains the time-honoured one: glucose.

In the treatment of diabetic acidosis it should be clearly understood that fructose administration in no way decreases the requirement for insulin. Fructose administration might, however, prove useful in diabetic acidosis for at least two reasons: (*a*) fructose represents a ready source of carbohydrate for the liver, and therefore one might expect a more rapid decrease in the excessive hepatic production of ketone bodies, (*b*) a larger proportion of fructose is almost immediately transformed into liver glycogen and other non-reducing metabolites (although a considerable portion, of course, is transformed into glucose); fructose might therefore be used to bring the tonicity of hypotonic salt solutions to normal, and thus facilitate their early administration without interfering quite as much as glucose with our ability to evaluate the adequacy of the blood sugar response to insulin. It remains to be seen, however, whether this will really prove of any practical value.—I am, etc.,

Boston, Mass. ALBERT E. RENOLD.

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2 *Bull. Johns Hopk. Hosp.*, 1941, **68**, 50.
3 *Diabetes*, 1953, **2**, 465.
4 Slein, M. W., *et al.* (1950). *J. biol. Chem.*, **186**, 763.
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6 Cori, G. T., *et al.* (1951). Ibid., **34**, 931.
7 *Biochim. Biophys Acta*, 1951, **7**, 304.
8 Hers, H. G. (1952). Ibid., **8**, 416.
9 —— and Kusaka, T. (1953). Ibid., **11**, 427.
10 Leuthardt, F., *et al.* (1953). *Helv. chim. Acta*, **36**, 227.

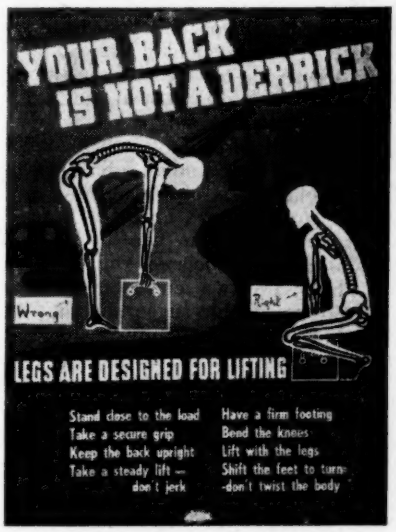
Acholuric Jaundice

SIR,—I was most interested in the article by Drs. J. L. Emery and D. W. Lemmon (*Journal*, March 27, p. 737) on "Crises in Congenital Spherocytic Anaemia (Acholuric Jaundice)." I have been following the case of acholuric jaundice in a medical man, in which, when he was a student, the condition used to remain quiescent until a spell of hard physical or mental activity. The condition would invariably appear a week or so before he sat for an examination, when he would develop a pale yellow, earthy colour. Cessation of work used to lead to regression of these symptoms, which would recur at the next period of mental stress. Haematological examination revealed the typical findings of acholuric jaundice. He has since had splenectomy, since when there has been a clinical cure, and no amount of mental or physical work produces any jaundice whatever.—I am, etc.,

London, S.W.3. DAVID THOMAS.

Advice on Weight-lifting

SIR,—Dr. M. E. M. Herford (*Journal*, March 20, p. 703) is right to stress the importance of showing men how to lift without damaging the back. The prophylaxis of lumbar disk lesions begins, however, not after the injury, but before. All men doing heavy work should have the mechanics of the lumbar joints explained to them and be taught how to avoid the initial damage, no less than a recurrence. He states that hospitals do not, in his experience, give this tuition. At the Department of Physical Medicine at St. Thomas's Hospital, a demonstration of the various ways of maintaining the lordosis during different types of work has been given by our physiotherapists in every relevant case for the past ten years. The first industrial body to illustrate the modern view on the prophylaxis of lumbar disk lesions[1] appears to have been the Workmen's Compensation Board of British Columbia, whose original poster is reproduced herewith.—I am, etc.,


YOUR BACK IS NOT A DERRICK
Wrong
Right
LEGS ARE DESIGNED FOR LIFTING
Stand close to the load
Take a secure grip
Keep the back upright
Take a steady lift — don't jerk
Have a firm footing
Bend the knees
Lift with the legs
Shift the feet to turn — don't twist the body

London, W.1. JAMES CYRIAX.

REFERENCE

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Chronic Pyelonephritis in Children

SIR,—In the past urinary infections in childhood have been treated much too lightly, and, as Drs. J. M. Stansfeld and J. K. G. Webb have shown (*Journal*, March 13, p. 616), for much too short a period. I am not convinced, however, that prolonged therapy, even using the broad-spectrum antibiotics, will prove successful, nor do I accept the arguments they use to explain why short courses of treatment so often fail.

Shortly after the war I studied a series of children of all ages who had had a proved urinary infection. The records are no longer readily available, but I recall that they comprised about 80 cases, of which over 70 were girls and almost every one had had at least two attacks. All the boys had demonstrable deformities in the renal tract. About eight of the girls, all with normal pyelograms, were liable to frequent recurrent attacks of urinary infection, and, at Dr. Charles F. Harris's suggestion, they were treated with prolonged courses of sulphonamides. The results were most disappointing and the treatment was eventually abandoned because so many of them developed staphylococcal infections whilst under treatment, whereas all the previous attacks had been due to *B. coli*. The new organism caused greater pain, dysuria, and fever, and was more difficult to eradicate than the old. Now that newer broad-spectrum antibiotics are available it is possible that prolonged therapy would be more efficacious, but clearly chloramphenicol would be too dangerous to use in this way; aureomycin might give rise to *B. pyocyaneus* infection in due course, and

hence terramycin would be the antibiotic of choice. No doubt Dr. Stansfeld is now using this drug, and his further experience will be awaited with interest.

The fact that the organism may change so readily with prolonged chemotherapy indicates a low resistance to infection in the renal tract and refutes the suggestion, made in the paper, that isolated foci of organisms, surviving in the kidney after the initial course of treatment, are responsible for the subsequent relapse.—I am, etc.,

Stock, Essex. IAN G. WICKES.

Adolescence and the Family Doctor

SIR,—Everyone who is interested in the health of the adolescent will welcome your leading article (*Journal*, March 27, p. 748) broadening and summarizing what has been constructive in the recent discussions in the medical journals. The problems of youth are indeed "many-sided and compelling," yet it is only one side which is really stressed by you as well as by most other contemporary writers on the subject. The eventual adjustment and mental health of the adolescent is obviously now one of our principal concerns, and it seems generally agreed that at least some of these young people need help in tackling the emotional disturbances associated with growing up.

There are two considerations which arise from your wholly reasonable suggestion that "this is surely above all the sphere of the family doctor." One is concerned with the ascertainment of the mental health problems of adolescence, the other with the treatment of psychiatric problems by the family doctor. First, I would like to be convinced that even a good family doctor will encounter anything like all the mental health problems of his adolescent patients unless he seeks actively for them. I fancy that the problems of adjustment of the type which you mention are not, in fact, regarded as *medical* problems by these young people in the same way as a boil or a sprained ankle for which advice is sought in the doctor's surgery. Some support for this comes from a rough analysis of the medical problems discovered among the adolescents in a recent study of the health of a small random sample of families in a London practice. Only one in five of the few "mental health" problems of these adolescents reached medical care. Secondly, even if he does encounter this mental ill-health which exists in his practice, and in spite of the admirable work of Dr. Michael Balint (*Journal*, January 16, p. 115) and the recommendations of several learned medical bodies,[1–4] the modern doctor still knows little or nothing of the psychotherapy which we are told is so badly needed. He knows something perhaps of what has been called the "technique" of support and reassurance (most of which he has picked up by trial and error), but I doubt that this is enough to give more than very superficial help to the adolescent or anyone else who is in trouble.

If the evidence of need is good and the psychotherapists know what they are talking about, then there is an increasingly strong case for an expansion of teaching about the medical care of the minor psychiatric disorders of all ages, and particularly about the adjustment problems of adolescence.—I am, etc.,

Belfast. E. MAURICE BACKETT.

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Single Incision for Bilateral Orchidectomy

SIR,—With reference to the letter by Mr. W. Skyrme Rees (*Journal*, April 3, p. 815), many years ago I learned, I think from Charles Donald, that the right approach to the testis is through the scrotum, and many years' experience of operation for hydrocele has confirmed the wisdom of that advice. Nature pushed the testicles into the scrotum; why pull them out, trim or enucleate them, and then push them back again?

Oozing may follow operations on the testis. It is harmless if there is a scrotal incision, but leads to a troublesome haematoma if there is not. Both testicles can be approached through an incision in the median raphe, and the final result after healing is the only known example of scarless surgery, the only perfect cosmetic result where cosmesis is unimportant.—I am, etc.,

London, N.W.8. HENEAGE OGILVIE.

Estimating Alcoholic Content of Body Fluids

SIR,—In the annotation on alcohol and road accidents (*Journal*, March 27, p. 749), I am surprised to read: "The more novel feature of the report is its discussion of estimating the alcoholic content of body fluids." This has been done for years in Sweden, and as long ago as 1936 I wrote an article on the subject which was published in your *Journal*.[1]—I am, etc.,

Bristol. H. K. V. SOLTAU.

REFERENCE

1 *British Medical Journal*, 1936, 1, 1048.

Medical Treatment of Peptic Ulcer

SIR,—In a leading article (*Journal*, March 13, p. 632) the results of medical treatment of chronic ulcer of the stomach are estimated as follows: "On the evidence, therefore, it would seem that the value of any form of dieting or of any drugs other than alkalis (and these only for the relief of pain) must be considered unproved." For about 40 years I have been engaged in the diagnosis and treatment of chronic gastric ulcers, and on the basis of my experiences I can at almost all points accept the editorial point of view. All the medicinal experiments that have been made with a "rational and even causal" treatment of peptic ulcer, for instance—with "novoprotein," L-histidine hydrochloride ("larostidin"), or different hormones, or the Sippy or Roentgen treatment—have proved disappointing with regard to the lasting effects, and the latest ulcer drugs, hexamethonium ("vegolysen") and methantheline ("banthine"), seem to get the same fate. Only the treatment with *large doses of bismuth* forms an exception.

This treatment was originally indicated, though in a somewhat primitive form, by Kussmaul and Steiner (about 1890), and subsequently taken up by Hayem and other French clinicians; they used the drug either in the pure state or in the less expensive, but also doubtless less effective, mixture composed of equal parts of bismuth, kaolin, and talc (*pansement bismutique*). Partly owing to the unmethodical use of this drug, partly because of the absence of an actual scientific basis (especially of efficient follow-up), the bismuth treatment was gradually brought into discredit. In Germany it seems to have been abandoned about 1930, and in France there has been a rapid decline of bismuth therapy, the interest being chiefly centred on "pathogenic ulcer therapy."[1] The treatment with large doses of bismuth appears to sink more and more into oblivion; it is not even mentioned in Bochus's impressive standard work *Gastroenterology*.[2]

About 30 years ago I took up the treatment of chronic gastric ulcer with large doses of bismuth carbonate, and during the last 20 years I have used this form of treatment in all my ulcer patients on the following principles: 10 g. of bismuth subcarbonate three times daily for the first two months, twice daily for the next two months, and for the last two months once daily before the principal meal. As the action probably depends upon a protective treatment of the gastric ulcer, it is of the utmost importance that the bismuth should be given on an empty stomach, 10 to 15 minutes before the meals. The simultaneous dietetic treatment commenced with a light puréed diet, gradually progressing to a normal light diet in the course of four to six months.

In 1948[3] and 1950[4] I published the results of an extensive research on this subject, based upon control examinations and follow-up of 400 patients with severe chronic ulcers, all with very pronounced roentgenologic changes, and in 60% with a duration of the disease of over five years. Apparently fresh ulcers with manifest bleeding were not included in this series of cases selected from a material of approximately 1,000 ulcer patients. In my 400 patients with gastric ulcer the *immediate results* were excellent, with rapid freedom from symptoms in the great majority (90%) of the cases, almost the same results ob-

tained in hospitalized patients (88%) and out-patients (83%) in six months. This observation is against the great importance which especially the psychosomatics attach to confinement to bed as an important sedative treatment in chronic peptic ulcer.

The permanent results—by far the most important point in estimating the efficiency of an ulcer treatment—are much better than could be expected: 41% of 400 patients were free from symptoms; these were cases of severe chronic ulcer, and the percentage is considerably higher than in the usual ulcer statistics. The freedom from symptoms applies to a great extent to the patients with the longest period of observation (10–16 years in 79 patients), where 31.6% were found to be free from symptoms, a lasting result which is far better than the usual one in medical treatment of gastric ulcer.

Practically similar results have been obtained by English authors, H. Avery[5] and F. Croxon Deller[6]; the latter concluded from his investigations that "bismuth subcarbonate takes pride of place in the modern treatment of ulcerative conditions of the stomach and duodenum—it is a most valued therapeutic weapon."—I am, etc.,

Hellerup, Denmark. SK. KEMP.

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[1] *Congrès des Sociétés Nationales de Gastro-enterologie*, 1948. Lausanne.
[2] *Gastroenterology*, 1947. Philadelphia.
[3] *Nord. Med.*, 1948, **40**, 1979.
[4] *Ugeskr. Læg.*, 1950, **112**, 1655.
[5] *Med. Press*, 1953, **229**, 579.
[6] *Med. Ill. (Lond.)*, 1952, **6**, 51

Dyspareunia

SIR,—The cause of this condition, a frequent source of frustration and despair in the newly married, is as a rule anatomic or psychogenic. The textbooks recommend ointments, stretching, dilators, operation, etc., but within the orb of every practitioner is a treatment which I have on many occasions found easy and immediately successful.

With the buttock raised upon a sandbag the small area to be dealt with is cleansed with ether and then painted with iodine. Shaving is not necessary. Using a very fine needle a weal is raised 3 cm. from the vaginal margin by the injection of 0.5 ml. procaine at 4, 6, and 8 o'clock to the fourchette. Through each of the 3 weals 5 ml. of warm "proctocaine" is deeply injected. After waiting a few minutes the vagina can be ironed out quite painlessly with three fingers. Success is 100%. Occasionally in the nervous, anxious type of patient it is advisable to induce anaesthesia with thiopentone, 0.5 g.—I am, etc.,

London, W.1. V. B. GREEN-ARMYTAGE.

Infectious Mononucleosis

SIR,—Dr. S. Shubert, Captain J. G. Collee, and Dr. B. J. Smith (*Journal*, March 20, p. 671) make a stimulating contribution to the study of infectious mononucleosis (glandular fever).

It would seem necessary, however, to emphasize that the term "sporadic" applied to cases of glandular fever may give a misleading conception of the disease. The term serves a useful purpose in distinguishing a group of cases, collected from different sources, in which the antibody is, by selection, of unquestionable degree and quality. This type of case has, as a rule, been selected from hospital records and is nothing more than a caricature of the cases seen in an epidemic, in many of which antibodies are of borderline diagnostic significance and in others entirely absent. As Tidy[1] points out, the disease is of low infectivity, but "if two or three cases develop in a school or closed community, a high proportion of the occupants tend to become infected"; and again,[2] "It is probable that the disease is infectious only in the early stages." By the time a single case is admitted to hospital cross-infection in a ward is rare. The following case, studied in an epidemic in 1952–3, illustrates these points.

An 18-year-old veterinary student, having spent a holiday at home where an epidemic of glandular fever was in progress, returned in good health to his studies at a university some 50 miles away. A week later he was off colour, and after a few days he reported sick with sore throat, frontal headache, and a stiff neck. He was admited to hospital, where the diagnosis of anginose glandular fever was confirmed, the heterophil antibodies reaching a dilution of 1/896 with positive absorption, and W.B.C. of 10,000 with 86% mononuclear cells. The staff, being unaware of the distant epidemic, took blood samples from the student's colleagues in a hostel, with entirely negative results. Thus an apparently "sporadic" case (and incidentally the most severe case in the epidemic) occurred in a town 50 miles away from the centre of the epidemic.

I maintain that so-called "sporadic" cases are merely the more severe forms which occur in any epidemic and indeed may be the only cases to be recognized in a mild epidemic. The difference lies in the degrees of infectivity, of symptomatology, of lymphocytosis, and of antibody formation. Glandular fever is primarily a disease of low infectivity, but widespread dissemination of infection is possible when other factors induce a hypersensitivity of a community to the cause. I hope to illustrate these points more fully at a later date.—I am, etc.,

Cupar, Fife. DAVID W. W. HENDRY.

REFERENCES

[1] *British Medical Journal*, 1952, **2**, 436.
[2] *Lancet*, 1934, **2**, 180.

SIR,—As one engaged in long-term investigation of infectious mononucleosis in a university population, may I make some comments related to the article by Dr. S. Shubert, Captain J. G. Collee, and Dr. B. J. Smith (*Journal*, March 20, p. 671)? The answer to their query "A Syndrome or a Disease?" is, I think, that the sporadic infectious mononucleosis is a syndrome and the epidemic glandular fever a disease. The suggested mechanism for the syndrome of lymphadenopathy, mononucleosis, and heterophil antibodies is that sensitization by a previous infection is required, whereon the "trigger action" is provided by reinfection at a suitable interval by the same or a closely allied organism. This agent may in many cases be that responsible for epidemic glandular fever, but it is likely that a heterogeneous group, viral, bacterial, and even protozoan, can produce similar results in a sensitized individual.

From experience of some 80 cases of infectious mononucleosis, I have seen several which could fit such a hypothesis, but in two instances there was a record of a recently previous blood examination. In both examples the first counts were done because of pharyngitis with enlargement of cervical lymph nodes suggesting mild infectious mononucleosis. In one patient the acute illness, with clear-cut mononucleosis and characteristic differential, occurred five months later, and in the other this took place after an interval of six weeks.

The serological tests seem an obstacle to the syndrome theory and have undoubtedly encouraged investigators to think in terms of a specific infective aetiology, but there is another viewpoint. At a conference of the British Student Health Officers' Association (Glasgow, July 6, 1953) I presented a progress report in which I claimed to have found a high correlation between the abnormal mononuclear count and the sheep cell agglutination titre of the serum from the same sample taken at or about maximum mononucleosis. This correlation was sufficiently high for the prediction of the agglutination titre, in the absence of Forssman antibody, with a reasonable degree of accuracy, the reciprocal of the titre being about one-tenth of the number of abnormal cells per cubic millimetre.

It seems that the antibody is simply a response to the presence of a special type of abnormal cell (of which a detailed account is in course of preparation). This possibility occurred to Paul and Bunnell[1] when they made their original contribution to the serology of infectious mononucleosis, and, if it can be established as a firm conclusion, the balance tips in favour of the syndrome concept, although the possibility that these cells produce or carry antibody specific for an unknown infective agent still remains. I am indebted to Collee, Shubert, and Smith for mention of Warren's paper, which I regret to say had escaped my notice. Warren[2] states that a positive Paul–Bunnell reaction only occurs when the curious lymphocytes of infectious mononucleosis form a large proportion of the differential count, an observation with which my own findings are in full accord.

Finally, I wish to underline the views of your contributors on the unsatisfactory nature of the simple agglutination reaction usually named the Paul–Bunnell test. There are at least 16 published articles representing over 100

cases where this test has been positive, even in titre as high as 1 in 2,560, in conditions other than infectious mononucleosis or serum disease. One wonders how many other strange cases, in which the former diagnosis has been made, properly belong to the same group.—I am, etc.,

Birmingham. J. C. BOWIE.

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1 *Amer. J. med. Sci.*, 1932, **183**, 90.
2 Ibid., 1941, **201**, 483.

Metabolic Stimulating Effect of Salicylate

SIR,—Dr. J. B. Cochran's paper "Further Observations on the Metabolic Stimulating Effect of Salicylate" (*Journal*, March 27, p. 733) is of interest in relation to a series of experiments on the "Effect of Certain Hydroxybenzoic Acids on the Oxygen Consumption of Wistar Rats" which I have recently reported.[1] To summarize the relevant data I found that salicylate had a stimulating effect, meta-hydroxybenzoic acid a depressant effect, and amongst the compounds which were inactive were para-hydroxybenzoic acid and 2:6 dihydroxybenzoic acid (γ resorcylic acid).

The results with the latter compound are of particular interest, since it has been reported[2] that γ resorcylic acid was beneficial in doses lower than those of salicylate necessary to achieve comparable clinical results. It would seem, therefore, important to know whether further experience with this drug has supported the original claims and, if so, has Dr. Cochran observed any metabolic stimulating effect in the human? If the original clinical claims are supported and the compound has no effect on the oxygen consumption of patients, then this metabolic effect would appear irrelevant to the treatment of rheumatic fever. If, on the other hand, the drug has not proved successful, then the rationale for introducing the drug, the ability of the anion to chelate, would seem to be fallacious.

It seems possible that the metabolic stimulating effect of salicylate has its origin in an uncoupling of oxidative phosphorylation similar to that which has been demonstrated in the case of dinitrophenols and related compounds.[3] Whether this is of any significance in elucidating the mode of action of salicylate in rheumatic fever must remain problematical. However, it is intended that the effect of salicylate on oxidative phosphorylation shall be studied elsewhere.—I am, etc.,

London, S.W.1. B. W. MEADE.

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1 *Ann. rheum. Dis.*, 1954. In press.
2 Reid, J., *et al.* (1951). *British Medical Journal*, 2, 321.
3 Judah, J. D. (1951). *Biochem. J.*, 36, 706.

Long-acting Penicillin on Haemolytic Streptococci

SIR,—It may be of interest to note the effect of a long-acting penicillin on the course of an epidemic of haemolytic streptococci, Type "A," in a residential school of 137 boys of 8 to 13 years of age. A nose and throat infection started at the end of January, and by February 9 28 boys were in the sick rooms with pyrexia and "positive" nose and/or throat swabs, and 12 others were either away from school or isolated but not diagnosed. On February 10 all the remaining boys and all of the staff had nose and throat swabs taken; 31 of these were "positive"—all boys—giving a carrier rate of nearly one in three of the remaining boys. It seemed likely that the school would shortly have to close down.

During the following three days, February 11 to 13, all of these boys and 16 adult staff were given a single intramuscular injection of 2 ml. of benzathine penicillin ("penidural") L.A. Throat and nose swabs taken five days and ten days or more later were "negative" in all except one boy, which was returned as "small numbers." There have been no further cases up to date. Reactions occurred in 17 boys within 24 to 48 hours of injection, 7 having pyrexia of 99° to 102° F. (37.2° to 38.9° C.), 8 nausea or vomiting, and 7 local induration or stiffness. Most of the 16 adults were very stiff, 5 felt "sick and miserable," and 3 had pyrexia. It seems probable that reactions are more likely to occur in those who are up and about. The cessation of the epidemic was more sudden and complete than had been hoped for. Whether this wholesale injection of infected and non-infected members of a community is more or less likely to produce insensitive strains of streptococci, I should like to hear argued.—I am, etc.,

Colwyn Bay. HERBERT LORD.

Bovine Tuberculosis

SIR,—We wish to clarify a point arising out of our report on bovine tuberculosis (*Journal*, February 13, p. 372), which is the subject of a letter to you by Drs. T. R. Maurice and Hugh Ellis (*Journal*, March 13, p. 646). In our report we employed the words "accredited tuberculin-tested herds" to convey the sense of officially recognized herds containing no reactors. Our choice of words was unfortunate, in that it permitted confusion to arise with the special designation accredited.

We do not believe the milk from such accredited herds to be safe, as in fact the herd responsible for our investigation carried this designation. We do, however, consider milk from herds of non-reactors—that is, carrying special designation tuberculin-tested—or pasteurized milk to represent a reasonable universal level of safety, and certainly to be more reliable than assuming consumers will always boil milk prior to use.—We are, etc.,

R. W. KIND.
Leicester. M. C. BROUGH.

Appendicitis in the Course of Measles

SIR,—Dr. W. H. Galloway's series (*Journal*, December 26, 1953, p. 1412) may appear apparently impressive, but only two of the seven operations seem justifiable to me on closer scrutiny of the case reports as submitted in the paper. The conclusion that the author derives from the series—namely, that symptoms of appendicitis during the course of measles warrant immediate operation—should not, I think, go unchallenged. I, with my limited experience in India, consider it my duty, in the cause of prevention of unnecessary appendicectomies, to raise my pen against it. Appendicular syndrome is fairly common in measles, and conservatism has proved successful in every case (about 15 in number) I have encountered so far. I do not deny the possibility of a fortuitous association of acute appendicitis with an attack of measles, and under these circumstances the case should be treated surgically on its merits. But such a coincidence is very rare and does not warrant the sweeping rule that a patient with measles showing appendicular syndrome should be operated on. On the other hand, my rule in practice has been that before diagnosing "surgical" appendicitis in a child, look in the mouth for Koplik's spots, and at the throat for congestion. If they are there, it is probably the "medical" appendicular syndrome not requiring a surgical intervention.

It does not mean thereby that the case should not be observed for acute surgical developments. As soon as there appears unequivocal evidence for the latter, surgical help should be called in. I may mention here some of the distinguishing features of the "medical" appendicular syndrome in measles: (1) associated flushed face, suffused eyes, and catarrh of the upper respiratory tract; (2) Koplik's spots on the buccal mucous membrane; (3) there is often leucopenia—occasionally there may be leucocytosis if the lungs show some inflammatory condition; (4) vomiting is often absent; (5) bowels tend to be normal or loose, but not constipated; (6) abdominal reflex on the right lower quadrant is often present; (7) the pain is more colicky in nature; and (8) comparatively little rigidity is present.

I have noticed a similar syndrome appearing in generalized urticaria when mucous membrane is probably involved as in measles. There also it is seen to respond to expectant line of treatment.—I am, etc.,

Poona City, India. P. L. DESHMUKH.

Dental Anaesthetics

SIR,—Dr. H. Newton-Andrews made a valuable contribution when he reported in the *Journal* (March 13, p. 641) the astonishing fact that he had seen sparks when the dentist's forceps slipped during the extraction of a tooth. I was therefore grateful to Dr. H. J. V. Morton when he suggested to me that he would, if I wished, investigate experimentally this unforeseen danger. Mr. Morton's experiments have already shown that sparks, visible in the dark, may quite easily be struck with certain dental forceps from extracted teeth, whether dry or wet and whether filled or unfilled. This observation has been confirmed by Mr. J. D. Robson, the dental surgeon at Salisbury with whom for some years I have been investigating the use of cyclopropane anaesthesia for extraction work. Dr. Morton has also shown in three patients that when anaesthesia was induced with a 50% mixture of cyclopropane and oxygen in the manner I have advocated[1 2] a sample of expired gases, even up to the sixth exhalation after withdrawing the anaesthetic, could be ignited by an electric spark.

Perhaps it is luck that in more than 2,000 administrations of cyclopropane for the extraction of more than 5,000 teeth I have had no mishap; or perhaps it is because the energy of these incandescent particles is not quite sufficient to detonate the explosive mixture. However that may be, it is now abundantly clear that this form of anaesthesia for extraction of teeth must at present be considered dangerous and abandoned until the matter has been more fully investigated.—I am, etc.,

London, S.E.1. J. G. BOURNE.

REFERENCES

[1] *Lancet*, 1952, 2, 705.
[2] Meeting of the Section of Anaesthetics, Royal Society of Medicine, February 5, 1954 See *British Medical Journal*, February 20, p. 452.

POINTS FROM LETTERS

Ulcerative Colitis

Mr. C. HORVITZ (London, S.W.1) writes: I was interested to read what Sir Robert Hutchison had to say about the operation of colectomy as performed by the late Sir Arbuthnot Lane (*Journal*, February 20, p. 454). I recall a certain occasion in my student days at Guy's Hospital on ward round with Lane. When confronted with a man who had a painful swollen wrist, he examined it for a few seconds, and then remarked to the class: "A clear case of auto-intoxication. We will remove his colon."

Smoking and Lung Cancer

Dr. G. G. SHERRIFF (London, W.8) writes: Is there necessarily any discrepancy between the fact that cancer of the lung increases with smoking or with life in towns, and the fact that it may occur in non-smokers? After all, smoking is an intensified and localized form of atmospheric pollution. One basic factor, then, would appear to be atmospheric pollution of various degrees and kinds.

Broken Milk-bottles

Dr. T. D. S. HOLLIDAY (Chester) writes: The danger of the dropped milk-bottle and its maiming effect on the hands, abdomen, and other parts of small children must be familiar to most doctors. The annual incidence of milk-bottle injuries in this country is probably considerable. Daily I view the quota of bottles huddled on the stone step with dread and my children with suspicion. Is it not possible for a better material to be used than glass? Would not waxed paper cartons be lighter and easier to transport, as well as safer than these slippery, dangerous bottles?

Telephone Manners

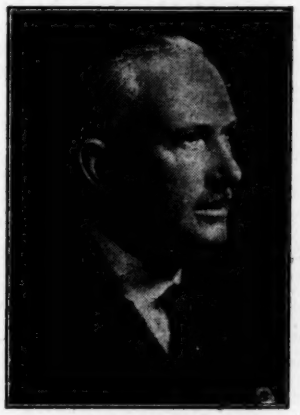
Dr. H. A. CONDON (Bromley, Kent) writes: I write to draw attention to a form of discourteous behaviour widely prevalent among hospital staff, both medical and administrative. I refer to the practice when making a telephone call of asking a secretary or the switchboard to find the desired person. The unfortunate recipient, on answering, is then kept waiting either while a search is made for the caller or until the caller is free to come to the telephone. This is no new problem—for example, it has been condemned by Hardy-Roberts (*Lancet*, 1951, 1, 1119) in an admirable lecture. However, the exercise of a little thought would soon abolish what is a most irritating practice.

Obituary

THOMAS CARNWATH, D.S.O., D.Sc., M.B., D.P.H.

Dr. Thomas Carnwath, who retired from the post of deputy chief medical officer to the Ministry of Health in 1940, died at his home at Whitehead, Northern Ireland, on April 2, after a long illness. He was 75 years of age.

Thomas Carnwath was born on April 7, 1878, the son of Mr. J. Carnwath, of Tyrone. From Foyle College, Londonderry, he went on to study medicine at Queen's University, Belfast, where he won a number of exhibitions and scholarships, and graduated M.B., B.Ch. with honours in 1903. After holding an appointment as demonstrator of anatomy at his own university he continued his postgraduate studies at Berlin University and at Hamburg, where he was an assistant in the Institute of Hygiene. He also held a post in Berlin as an assistant in the Imperial Board of Health. On his return to Britain he took the Cambridge D.P.H. in 1906, and was then appointed assistant medical officer of health of Manchester, and later deputy medical officer of health. He then joined the staff of the Local Government Board as a medical inspector, and about this time he was appointed lecturer in public health at St. Thomas's Hospital. On the outbreak of the first world war he joined the R.A.M.C., and was for a time attached to the Honourable Artillery Company. He was mentioned in dispatches, and in 1918 was awarded the D.S.O. By the time he returned to civilian life the Ministry of Health had taken the place of the Local Government Board, and Carnwath immediately became busily engaged in the many medical activities of the Ministry. In 1929 he was promoted to senior medical officer, and in 1935 he became deputy chief medical officer. At the Annual Meeting of the B.M.A. in 1934 he was president of the Public Health Section, and three years later president of the Section of Medical Sociology. In 1935 he was awarded the honorary degree of D.Sc. by Queen's University. After his retirement in 1940 he went to live in Northern Ireland, where, among other activities, he helped to carry out an investigation of the public health services of Belfast.



[*Elliott & Fry, Ltd., London*

Apart from the numerous official reports of which he was the author, Dr. Carnwath, during the early stage of his career, had written a number of papers on public health subjects, some of which were published in German medical journals. He was an examiner at the Universities of London, Manchester, Birmingham, and Belfast, and a member of the Board of Studies in Hygiene and Public Health of the University of London and of the Senate of Queen's University, Belfast. In addition, he served on the Army Hygiene Advisory Committee and the National Radium Commission.

Dr. Carnwath married Margaret Ethel, only child of the late Andrew M'Kee, of Belfast, who survives him together with two sons.

We are indebted to Sir ARTHUR MACNALTY for the following appreciation: May I be allowed to pay a tribute to my friend and former colleague, Thomas Carnwath? After a distinguished career at the Queen's University, Belfast, postgraduate study in Germany, and as deputy medical officer of health at Manchester, he became a medical inspector at the Local Government Board. It was a most interesting time, for the health services—tuberculosis, maternity and child welfare, and venereal diseases—were being planned and organized under the direction of Sir Arthur Newsholme. Then the first world war broke out, and Carnwath immediately joined the R.A.M.C.(T.F.). He came back to us in 1918 with a D.S.O. and resumed work in public health under his immediate chief, Sir George Buchanan. International health work, the Radium Commission, with many other activities, fully occupied him at the Ministry of Health. In each and all of them he did excellent though often inconspicuous work, and I was both honoured and pleased that he became Deputy Chief Medical Officer when I was appointed Chief Medical Officer of the Ministry in 1935. Those were strenuous days, for war threatened, and we had much to do in preparing for it. We were often working at the office until midnight. Carnwath had a serious illness just before the outbreak of war, and, though for a time he struggled gallantly on, the Ministry lost his valuable services early in 1940. In retirement his health improved, and he rendered services to Northern Ireland as an elder statesman of public health.

At the Ministry we liked Carnwath not only for his great abilities, but for his invariable kindness, goodness of heart, wit, and humour. The sympathy of his many friends goes out to Mrs. Carnwath and their two sons.

Medical Notes in Parliament

HOSPITAL DOCTORS' PAY

Mr. JACK BROWNE (Govan, Con.) asked the Minister of Health on April 8 whether the Medical Whitley Council had yet reached agreement on the pay of hospital medical staff. Mr. IAIN MACLEOD replied that an agreement had just been reached. He then gave the details issued by Committee "B" of the Medical Whitley Council and published in the *Supplement* of April 10 (p. 145). After saying that details of the new arrangements were being worked out by the two sides of Committee "B," the Minister added that he and the Secretary of State for Scotland had told the committee that they were prepared to approve the agreement. Its cost would be about £3,250,000 in a full year.

Consultants' Expenses

Mr. A. A. H. MARLOWE (Hove, Con.) asked the Chancellor of the Exchequer what consultations had taken place between the Treasury and the Ministry of Health with regard to the expenses of hospital consultants employed in the Health Service which were not deductible for income-tax purposes; whether he was aware that consultants incurred many expenses for which they could make no income tax rebate claim on Schedule E assessments; and whether he would introduce legislation to remedy this hardship.

Mr. J. A. BOYD-CARPENTER, the Financial Secretary, replied on April 8 that hospital consultants were, like other employees, assessable under Schedule E, and the same rules with respect to expenses applied to them as to other taxpayers so assessed. He saw no reason to propose legislation giving them preferential treatment. The general question of what expenses were admissible to such taxpayers was within the terms of reference of the royal commission.

Mr. MARLOWE said there was a conflict between the appointing authorities, who would not appoint a consultant unless he had a motor-car, telephone, and secretary, and the Revenue authorities, who would not allow these expenses. A consultant therefore had necessarily to incur expenses which he could not deduct for tax purposes. Mr. BOYD-CARPENTER said the broad question was within the reference to the royal commission. He could not see any justification for treating these persons for tax purposes differently from other taxpayers.

Mr. H. M. KING (Southampton, Lab.) urged that consultants were not treated the same as general practitioners for this purpose. Would the Financial Secretary try to make an adjustment as between them? Mr. BOYD-CARPENTER said that sort of question was for the Minister of Health. He was only concerned with administration of the tax law. Mr. MARLOWE gave notice of his intention to raise the matter again.

Transfers to Part-time Service

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) was informed by Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, that in 1951 the number of consultants employed by regional boards who transferred from whole-time to part-time service was 42, in 1952 it was 61, and in 1953 it was 46.

Defects of Welfare Services

The subject of debate in the House of Lords on April 7 was a resolution laying the blame for many of the failures in the welfare and health services on imperfect co-ordination between the various authorities concerned, and declaring that greater local discretion, financial and administrative, would result in better service at less cost.

Lord SALTOUN, introducing it, emphasized that he was not seeking to attack individuals but to correct the system. In the past three years there had been a trend towards crystallization in the various services, and the marking of boundaries between the various branches of what should be a common service. The motto should not be "Trespassers will be prosecuted" or "Over to you." But so many different authorities were concerned that some sort of co-ordination was difficult, and complete harmony at all times little short of a miracle. He suggested that a small committee should examine the services to find out how better co-ordination could be achieved, and to make a quick report.

Lord MATHERS suggested the possibility of a closer integration of the specialist and general-practitioner services by a closer linking of the functions of executive councils with the regional hospital boards. He was critical of the way in which many senior members of hospital staffs, he said, concentrated their work into the early part of the day; this might even involve duplication of staff to meet peak demands, while later in the day theatres might be empty and unused.

Lord Beveridge's Criticisms

Lord BEVERIDGE deplored the failure to establish health centres—there were three mentioned in the Ministry of Health report for 1952, and one or two others had come along since. The institution of health centres was proposed long before 1946, in an interim report of the B.M.A. Planning Commission, which set out a detailed scheme. Health, and the proper provision for it, would become soon even more important than houses. He pressed the Government to get "this dream, and main intention of the 1946 Act, put into reality. He criticized as inappropriate to a Health Service the Treasury rule of annual budgets, which meant hasty spending towards the end of a year, or the return of unexpended resources; and, going further, questioned whether a Minister and a Civil Service department was the right organ for running this national industry to secure for the people the means to health.

The EARL OF CRANBROOK, a regional hospital board chairman, said the machine could be made to work, by co-operation at every level. The members of various bodies were all drawn from people with an interest in local administration; many people sat on more than one body, and so secured a good deal of integration of policy.

Lord AMULREE said there were probably enough hospital beds for the sick if proper use was made of them. In 1948 a committee called together by the B.M.A. issued a very good report,[1] propounding practical and economical means, but nothing had been heard of it since. What was needed was free exchange between welfare institutions and the hospitals. The encouragement of domiciliary services for the benefit of the infirm and the frail was very important. According to the census figures, in 1901 the total number of people in the medical and auxiliary services was about 3,000 per million of the population. In 1951 it had risen to nearly 10,000 per million. That was rather alarming, because it showed that the supply was going to dry up.

Lord CALVERLEY said that the kingpin of the Health Service was the general practitioner. He was only heard of when he had made a mistake.

Desire for Improvements

Lord MANCROFT, a Lord-in-Waiting, was prepared to accept the spirit of the motion, but not the letter. There was no official façade and satisfaction about the services, he said, but a constant desire on the part of the Government for improvements. Co-ordination of the different parts of these services was one of the greatest single problems of the Health Service, but it was only emphasized and not created by the Service itself. Co-operation eventually rested on human relationships and personalities rather than on drastic reorganizations. Health centres were expensive to build, and had not been as popular either with patients or with doctors as had been expected. An alternative that presented itself was the establishment by doctors of group practices. This development was supported by the Minister, and was being encouraged by the offer of interest-free loans to doctors to acquire or convert buildings to establish a group practice. His general answer to the debate, however, rested on the fact that most of the subjects it covered were within the terms of reference of the Guillebaud and Phillips committees investigating the Health Service, and half-way conjectures from him would not be helpful. The motion was withdrawn.

College of Physiotherapy

Miss PAT HORNSBY-SMITH, Parliamentary Secretary, Ministry of Health, stated on April 8 in answer to Mr. F. J. ERROLL (Altrincham and Sale, Con.) that the Minister of Health would not give recognition to the British College of Physiotherapy under the terms of the N.H.S. (Medical Auxiliaries) Regulations, 1954.

Welfare Foods

Mr. JOHN RODGERS (Sevenoaks, Con.) asked the Minister of Food on April 6 what arrangements would be made for the local distribution of welfare foods, other than liquid milk, when the local offices of his department were closed later in the year. Major G. LLOYD GEORGE stated that the local health authorities had been invited to take over responsibility for these arrangements as part of their duty under the National Health Service Acts to provide for the care of expectant and nursing mothers and young children. The associations of authorities covering England and Wales had already agreed to do so.

Power Station Flue Gases

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Fuel and Power on April 5 whether, in view of the limited possibilities of existing processes for ridding the flue gases of power stations of harmful sulphur oxides, he would arrange for investigation and research into the matter. Mr. GEOFFREY LLOYD answered that it was already the subject of continuous research. Mr. HASTINGS pressed for special attention to the matter, saying that the present methods required large quantities of water, and the River Thames would be saturated with the effluent of calcium sulphate when only two of the power stations on its banks were in use. Mr. LLOYD agreed that the limit had been reached with this effluent, and said that work was in progress on a new process involving the use of gas works liquor, but it was in an experimental stage.

Mr. HASTINGS also questioned the Minister about the additional amount of sulphur oxides that would be discharged from the proposed extension to the Bankside power station, and what methods were proposed for eliminating them from the flue gases. Mr. LLOYD told him that a steady decrease in fuel consumption was expected from now onwards, and the discharge of sulphur oxides would therefore be reduced. The new part of the station would disperse its oxides at high temperature and great velocity through chimneys 375 ft. high.

[1] *Supplement*, August 7, 1948, p. 71.

Gas Workers' Risks

Mr. GEOFFREY LLOYD, Minister of Fuel and Power, informed Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) that the West Midland Gas Board employed three full-time and a number of part-time medical officers. The question of *x*-ray examinations of the employees, and at what intervals, was part of the board's day-to-day administration on which he was asking the chairman to write to Dr. Stross.

Dr. STROSS asked the Minister to bear in mind the work of the Medical Research Council on the specific risks which gas workers had to undergo, especially in cancer of the lung. Would he see that as far as possible all gas boards provided ample medical services for their workers? Mr. LLOYD replied that he had brought the matter to the attention of the gas boards, and impressed on them the importance of medical services.

Average Cost of Prescriptions

In reply to Mr. VAUGHAN-MORGAN (Reigate, Con.), on April 8 Miss PAT HORNSBY-SMITH gave the following Table showing the average cost per prescription in England and Wales for each month since June, 1952, and for the comparable period before June, 1953.

June, 1950, to February, 1952		June, 1952, to February, 1954		
1950	d.	1952	d.	
June	39·47	June	49·92	
July	39·81	July	50·33	
August	40·14	August ..	50·42	
September ..	39·65	September ..	49·21	
October ..	38·71	October ..	49·00	
November ..	39·02	November ..	49·79	
December ..	39·55	December ..	49·68	
1951		1953		
January ..	37·09	January ..	48·12	
February ..	40·49	February ..	47·30	
March	42·50	March ..	48·79	
April	43·81	April	50·50	
May	44·88	May	50·66	
June	45·86	June	50·61	
July	46·55	July	50·88	
August	47·33	August ..	48·92	
September ..	46·31	September ..	47·82	
October ..	45·31	October ..	47·09	Estimates obtained from sample
November ..	46·02	November ..	47·49	
December ..	46·58	December ..	49·22	
1952		1954		
January ..	46·51	January ..	48·48	
February ..	47·27	February ..	48·80	

£5,000 Then and Now

Mr. C. OSBORNE (Louth, Con.) asked the Chancellor of the Exchequer on April 6 the net income of a married man with two children in 1935 who received a gross income of £5,000 a year; what it would be to-day; and what it would amount to to-day allowing for the depreciation in the value of the £ between 1935 and to-day. Mr. J. A. BOYD-CARPENTER, Financial Secretary to the Treasury, replied that a gross earned income of £5,000, in the case of a married man with two children, produced a net income, after deduction of tax, of £3,687 in 1935–6 and £2,689 in 1953–4. The latter amount was equivalent in purchasing power to about £1,090 in 1935–6.

Medico-Legal

SPINAL ANAESTHETICS APPEALS FAIL

The Court of Appeal on April 8 dismissed the appeals of two men who became paralysed below the waist after they had been given spinal anaesthetics (nupercaine) contaminated with phenol antiseptic in 1947. Mr. C. H. Roe, aged 51, and Mr. Albert Woolley, aged 62, had claimed damages from the Ministry of Health and Dr. J. Malcolm Graham, the anaesthetist. Mr. Justice McNair, who had dismissed the actions, holding that the hospital theatre staff and the doctor were not negligent, found that the nupercaine had been contaminated by phenol getting into ampoules.[1] General damages had been provisionally assessed at £15,000 for Mr. Roe and £10,000 for Mr. Woolley.

Lord Justice Somervell said that the question was whether the percolation of phenol solution into ampoules was caused by the negligence of the defendants or either of them. Dr. Graham, who appreciated the possibility of cracks in ampoules, said that he examined each one carefully and he did not believe that he could have missed a crack. The judge accepted his evidence. The finding that the hospital authorities and Dr. Graham were not negligent was justified. The fact that something went wrong was not proof of negligence. There were obvious risks in surgical operations.

Lord Justice Denning said that no one could be unmoved by the disaster of these two men. The facts called for an explanation by the hospital authorities and Dr. Graham, and they had given one. They had spared no trouble or expense to seek out the cause of the disaster. There was a danger that ampoules might become cracked, and the cracks might be so fine that they could not be detected by ordinary inspection. The carbolic disinfectant in which the ampoules were kept would then seep through the cracks into the nupercaine, and no one would realize that it had taken place. That was the explanation of the disaster, and the question was whether any of the staff were negligent. Medical science had conferred great benefits on mankind, but those benefits were attended by considerable risks. Every surgical operation was attended by risks. Dr. Graham sought to escape the danger of infection by disinfecting the ampoule. In escaping that known danger he unfortunately ran into another danger. He did not know that there could be undetectable cracks, but it was not negligent for him not to know it at that time. "We must not look at this 1947 accident with 1954 spectacles," said his lordship. "The judge acquitted Dr. Graham of negligence, and we should uphold his decision." Never again, it was to be hoped, would such a thing happen. It was the extraordinary accident to these two men which first disclosed the danger. Nowadays it would be negligence not to realize the danger, but it was not then. These two men had suffered such terrible consequences that there was a natural feeling that they should be compensated, but we should be doing a disservice to the community if we were to impose liability on hospitals and doctors for everything that happened to go wrong. "Doctors would be led to think more of their own safety," he continued, "than of the good of their patients. Initiative would be stifled and confidence shaken. A proper sense of proportion requires us to have regard to the conditions in which hospitals and doctors have to work. We must insist on due care for the patient at every point, but we must not condemn as negligence that which is only a misadventure."

Lord Justice Morris also agreed that the appeals failed.

No order was made as to costs. Leave to appeal to the House of Lords was refused.

The Medical Defence Union instructed Messrs. Hempsons to act for Dr. Graham.

[1] *British Medical Journal*, November 21, 1953, p. 1165.

LACK OF HOSPITAL–G.P. LIAISON

A report has been published of an inquiry into the unsuccessful attempts of a general practitioner to gain admission to hospital for a patient dying of haemorrhage. Failure to secure admission was due to a number of circumstances, reports the investigating committee, which had been appointed by the Birmingham Regional Hospital Board. Its findings were as follows.

First, the general practitioner should have used the bed bureau. If he had, admission would have been obtained. Secondly, Wolverhampton Hospital Management Committee failed to communicate the proper arrangements to the medical staff, and the house-physicians did not know that refusal to admit could be decided only by the senior resident officer or the consultant on call. Thirdly, no real effort was made to impress upon two hospitals the seriousness of the case. The committee states that liaison between the hospital group and the general-practitioner service needs to be improved. Among the administrative recommendations to ensure that such a case shall not recur the committee recommends that refusal to admit to hospital shall not be based on lack of beds: extra beds must be put up.

Vital Statistics

Infectious Diseases

The largest increases in the notifications of infectious diseases in England and Wales during the week ending March 27 were 210 for scarlet fever, from 1,282 to 1,492, and 191 for dysentery, from 1,124 to 1,315, and the only large decrease was 258 for measles, from 2,325 to 2,067.

A small rise in the incidence of scarlet fever occurred in every region. The largest rise was 53 in London, from 41 to 94. 2,553 cases of whooping-cough, 10 more than in the previous week, were notified, and the largest fluctuations in the local returns were increases of 37 in Norfolk, from 39 to 76, 37 in Warwickshire, from 116 to 153, and 30 in Kent, from 120 to 150, and decreases of 39 in Cornwall, from 68 to 29, and 36 in Yorkshire West Riding, from 179 to 143. The chief variations in the trends of measles were an increase of 95 in Staffordshire, from 169 to 264, and decreases of 70 in Cheshire, from 160 to 90, and 42 in Norfolk, from 467 to 425. 14 cases of diphtheria, 4 fewer than in the preceding week, were notified.

The number of notifications of paratyphoid fever decreased by 25, from 45 to 20. This fall was contributed by Wales, where the notifications declined from 44 to 17.

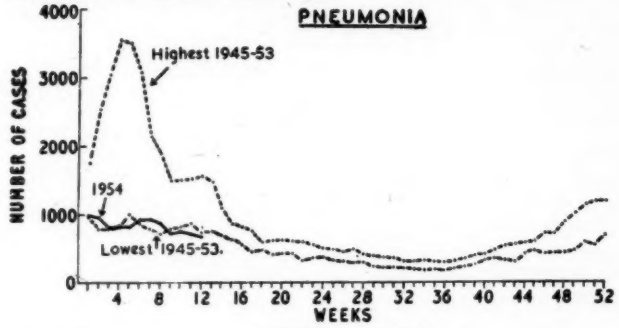
24 cases of acute poliomyelitis were notified during the week. These were 2 more for paralytic and 3 more for non-paralytic cases than in the preceding week. The only administrative areas with 2 cases were Gloucestershire, Bristol C.B., and Staffordshire, Cannock U.D.

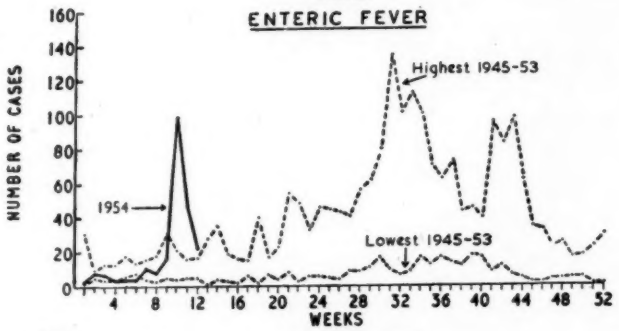
For the fourth consecutive week the number of notifications of dysentery has exceeded 1,000. The largest returns during the week were Lancashire 229 (Salford C.B. 50, Bolton C.B. 45, Eccles M.B. 18, Preston C.B. 15, Manchester C.B. 14, Southport C.B. 14, Ormskirk U.D. 14, Liverpool C.B. 11), London 194 (Islington 65, Lewisham 31, Shoreditch 19, Stepney 11, Finsbury 10), Yorkshire West Riding 159 (Bradford C.B. 48, Keighley M.B. 29, Leeds C.B. 28, Dewsbury C.B. 24), Middlesex 101 (Southall M.B. 21, Hornsey M.B. 19, Enfield U.D. 16, Willesden M.B. 11), Leicestershire 100 (Leicester C.B. 100), Essex 58 (Romford U.D. 16, West Ham C.B. 10), Kent 54 (Sevenoaks R.D. 24), Devonshire 53 (Exeter C.B. 28, Great Torrington M.B. 17), Norfolk 45 (Norwich C.B. 45), Surrey 43 (Epsom and Ewell M.B. 21, Carshalton U.D. 15), Nottinghamshire 42 (Nottingham C.B. 23, Beeston and Stapleford U.D. 18), Warwickshire 39 (Birmingham C.B. 34), Staffordshire 35 (Cannock U.D. 21), and Berkshire 24 (Maidenhead M.B. 20).

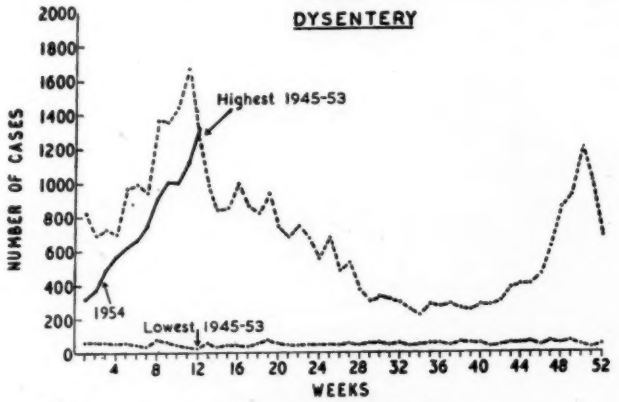
In Scotland the number of notifications of dysentery increased from 276 to 366.

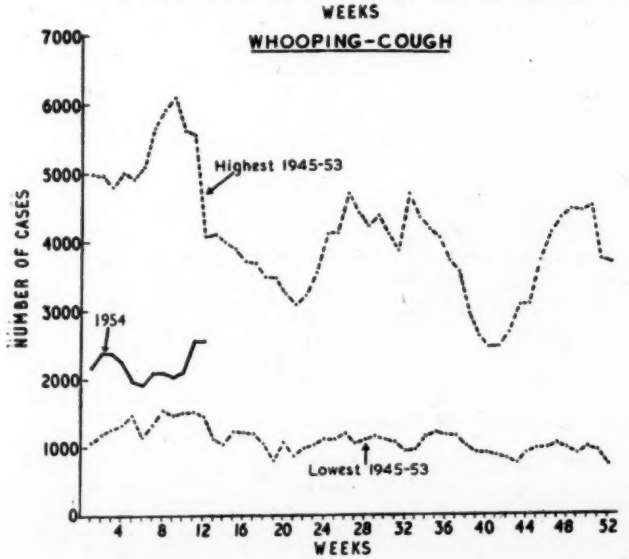
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 27** (No. 12) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	14	0	9	1	0	20	1	13	3	
Dysentery	1,315	194	366	2	23	463	79	120	5	
Encephalitis, acute	6	3			0	6	0	0	0	
Enteric fever:										
Typhoid	2	0	0	1		2	0	0	0	2
Paratyphoid	20	0	0	1		5	0	0	0	0
Food-poisoning	130	17		0		60	7		0	
Infective enteritis or diarrhoea under 2 years				14	11				13	11
Measles*	2,067	32	176	32	452	25,791	1133	479	176	254
Meningococcal infection	35	4	17	4		44	5	25	4	1
Ophthalmia neonatorum	34	3	11	0		39	5	6	0	
Pneumonia†	661	41	222	12	9	1,067	64	365	27	5
Poliomyelitis, acute:										
Paralytic	15	1	4	0		42	9	1		2
Non-paralytic	9	0				4	0			
Puerperal fever§	233	43	3	1		241	15	16	0	
Scarlet fever	1,492	94	166	38	35	1,739	111	207	42	58
Tuberculosis:										
Respiratory	785	92	147	29				201	25	
Non-respiratory	95	5	21	5				28	2	
Whooping-cough	2,553	93	466	30	58	3,202	260	372	59	158

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	1	0	0	0	0	0
Dysentery	0	0		0		0	0	1	0	
Encephalitis, acute			0		0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	3	0	4	19	2	3	4	1
Influenza	22	3	1	0	0	100	6	7	3	2
Measles			0	0	2		0	0	0	0
Meningococcal infection		0	0				0	1		
Pneumonia	257	35	27	7	7	369	59	28	23	15
Poliomyelitis, acute	1	0			0	7	2			0
Scarlet fever			0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	96	14	16	4	12	137	20	16	5	9
Non-respiratory			3	0	2		3	2	0	2
Whooping-cough	2	0	0	0	0	7	1	0	0	0
Deaths 0–1 year	270	30	30	9	14	301	35	30	13	22
Deaths (excluding stillbirths)	5,906	836	706	128	188	6,489	943	651	146	213
LIVE BIRTHS	8,346	1233	931	257	378	8,163	1223	990	249	484
STILLBIRTHS	210	22	21			218	26	26		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

British Pharmaceutical Industry.—The annual dinner of the Association of British Pharmaceutical Industry was held on April 7, the president, Mr. C. L. Saul, being in the chair. In proposing the toast, "The Pharmaceutical Industry," Miss Pat Hornsby-Smith, M.P., Parliamentary Secretary, Ministry of Health, said that in the field of British enterprise it was a great industry. "You command a high standard for your products and show the world—particularly in those of your companies that have vast research enterprises besides their manufacturing processes—that you have a standard in which we in the Ministry of Health share your pride." Their keenest competitor in the world markets, Miss Hornsby-Smith continued, was a rehabilitated Germany "working like a beaver." The Ministry was grateful to the industry for the unfailing co-operation it had given in dealing with inquiries as to cost and calls for economy. The prescription side of the N.H.S. bill was about £35m. out of a total of £400m., the biggest single item being £280m. for the hospital service. The general practitioner had the last word in saying what should go on the prescription, and could make the biggest single contribution to economy, "because you in your industry merely provide the goods which he is responsible for ordering." Miss Hornsby-Smith said she thought that "such abuse and extravagance as there is lies not in the highly expensive drugs which are vital in particular and limited cases, but in the overprescribing of the small common articles—the cotton-wool, the lint, and the like." Referring to inquiries into costings and price, Miss Hornsby-Smith said that if the State was to fulfil its obligation to the public and the taxpayer they had to be able to assure the Public Accounts Committee "that we as a Ministry were satisfied that the prices charged in whatever sphere of your industry were right, proper, and justified." Mr. Saul proposed the health of the guests, to which Mr. A. E. W. Thomas, the editor of *The Listener*, made a most happy and witty response.

Food Production in East Africa.—A most successful three-day conference on the "Medical, Agricultural, and Veterinary Aspects of Food Production in East Africa" was recently held at Makerere College Medical School, Uganda, under the presidency of Sir Bernard Keen, F.R.S. The conference was organized by the East African Advisory Committee on Medical Research, and attended by doctors and experts on agriculture and local custom. Speaking in his opening address on the future of the Colonial Territories, the Governor of Uganda, Sir Andrew Cohen, stated his belief that their standard of living would be determined by no one more than those engaged in research. "We can no longer rely," he said, "on hit-and-miss methods and *ad hoc* solutions." During the discussions the medical workers pointed to the widespread existence of calorie and protein deficiency, particularly in the weanling child. A great increase in food production was needed—quantity not quality. In their answer the agriculturists emphasized the great inefficiency in the use of existing resources and the vast scope for improved production by relatively simple methods. One of the crucial questions was the shortage of man-power. There was evidence that East Africa was underpopulated, and only the best land was being used. Industrialization was in danger of preceding the agrarian revolution which alone could sustain it. Among the visitors from Britain to the conference were Professor A. C. Frazer (Birmingham), Professor P. C. C. Garnham (London School of Tropical Medicine), and Dr. R. Lewthwaite (Colonial Office).

Hostel for the Borderline Case.—On March 30 Sir Henry Cohen and the Bishop of Liverpool, Dr. Clifford Martin, opened an experimental hostel at Sefton Drive, Liverpool. The hostel, which is directly administered by the Liverpool Personal Service Society, provides accommodation for 38 patients. The Liverpool Regional Hospital Board has entered into contractual arrangements for the use of 18 of the beds for patients who are transferred from hospital while still requiring medical and nursing care but who are as yet not fit for discharge to their own homes. The remaining 20 beds are available to the local health authority for patients who are aged and frail but who do not require medical and nursing care. The hostel is experimental in nature, and it is hoped that experience of its use will do much to answer many of the questions about those borderline cases which are neither fully the responsibility of the hospital service nor yet fit enough to be cared for in the type of hostel provided by the local health authority under Part III of the National Assistance Act.

Henry Simpson Newland Prize in Surgery.—The first award of this triennial prize to commemorate the services of Sir Henry Newland to the medical profession, particularly in Australia, will be made in 1955. The prize, offered by the Federal Council of the B.M.A. in Australia, will consist of £100 and a medal. It will be given for the best essay on "The Influence upon Surgical Practice of Irradiation and Endocrine Therapy." Essays, typewritten or printed in English, must be based on personal observation and experience, and not exceed 50,000 words in length. The prize essay will be submitted to the editor of the *Medical Journal of Australia*. The competition is open to any graduate of a medical school within the British Commonwealth. The closing date for the receipt of essays is May 20, 1955. Further information may be obtained from the general secretary of the Federal Council, 135 Macquarie Street, Sydney, Australia.

Hunterian Society Essays.—Dr. J. Lipsey, of Littlehampton, Sussex, has been awarded the Hunterian Society's Gold Medal for his essay in last year's competition. The subject was "The Management of Peptic Ulceration in General Practice." A *proxime accessit* award was made to Dr. B. C. Zoob, of Battersea. The subject for this year's essay is "Management of the Climacteric in General Practice." The competition is open to all general practitioners, and the closing date for entries is December 31. Further details may be obtained from the honorary secretary, Mr. Alec W. Badenoch, 110, Harley Street, London, W.1.

Nuffield Grant to Walter and Eliza Hall Institute.—The Nuffield Foundation has given £12,000 to the Walter and Eliza Hall Institute in Melbourne, Australia, for research into inherited elements in the more common human diseases. The gift is an outcome of discussions between the director of the Institute, Sir MacFarlane Burnet, F.R.S., and representatives of the Foundation.

Overseas Plastic Surgeons in Britain.—Twenty plastic surgeons coming from Austria, Belgium, Denmark, Egypt, Finland, France, Germany, Italy, and Portugal have just completed a two weeks' course at the Plastic Surgery and Jaw Injuries Centre of the Queen Victoria Hospital, East Grinstead. The course was directed by Sir Archibald McIndoe and arranged by the British Council.

William Hyde Award.—Miss P. C. Colson has recently received the William Hyde Award for 1952. Miss Colson is general secretary of the Central Council of Physical Recreation. The award is made by the Research Board for the Correlation of Medical Science and Physical Education, and is valued at £300.

Dr. F. E. Camps has been appointed to the part-time university readership in forensic medicine tenable at the London Hospital Medical School.

Dr. G. E. Francis has been appointed to the university readership in biochemistry tenable at St. Bartholomew's Hospital Medical School, London.

COMING EVENTS

Professor Henry K. Beecher, of Harvard, will deliver the Macarthur Postgraduate Lecture in the Surgery Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, on May 5 at 5 p.m. His subject will be "Resuscitation and Other Early Care of the Severely Wounded Man."

Professor Gerhard Domagk will deliver the Cameron Prize Lecture in the Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, on May 6 at 5 p.m. His subject will be "The Development of Chemotherapy in Tuberculosis."

St. John Ambulance Brigade: Surgeons' Weekend Conference.—A conference and dinner for surgeons of all ranks, nursing officers, and non-medical officers nominated by their surgeons will be held at the Cairn Hotel, Harrogate, from April 23 to 25. Further information from the Department of the Surgeon-in-Chief of the Brigade, 8, Grosvenor Crescent, London, S.W.1.

Renal Association.—The annual general meeting will be held at the Ciba Foundation, 41, Portland Place, London, W.1, on May 28 at 4.30 p.m. Mr. I. H. Griffiths will speak on "Renal Arteriography," and Dr. Robert Gaunt on "Studies on the Experimental 'Eclampsia-like' Syndrome."

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Tuesday, April 20

SOCIETY FOR THE STUDY OF ADDICTION.—At 11, Chandos Street, W., 8 p.m., 70th annual meeting. Mr. Derek Curtis-Bennett, Q.C.: Alcoholism and the Law.

Wednesday, April 21

OXFORD UNIVERSITY.—At Department of Human Anatomy, 2.15 p.m., demonstration by Professor P. Stohr (University of Bonn): Morphology and Pathology of the Vegetative Nervous System.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. L. H. Savin: Ophthalmic Neurology (3).

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. C. Worster-Drought: Speech Disorders in Children of School Age.

Thursday, April 22

CHADWICK TRUST.—At 26, Portland Place, W., 5.30 p.m., Dr. C. Banning (Netherlands): Ante-Natal, Natal, and Post-Natal Care in the Netherlands.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Chase Farm Hospital, Enfield, 3.15 p.m., clinical meeting. Members of Enfield and Potters Bar and North Middlesex Divisions, B.M.A., are invited.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor D. J. Browne: Principle of Controlled Movement in Orthopaedics.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Myopia, and the Care and Treatment of the Myopic Patient.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Mr. J. Bruce: Surgery of the Small Intestine.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., neurology demonstration by Dr. D. J. Williams.

Friday, April 23

OSLER CLUB OF LONDON.—At 11, Chandos Street, W., 7.45 p.m., Marie Stopes, Ph.D.: History of Contraception.

Saturday, April 24

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Middlesex Hospital, 2.30 p.m., clinical meeting in Radiotherapy Department.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Harper.—On April 3, 1954, to Dr. Marita Harper (formerly Shattock), wife of Dr. Eric Harper, of Swindon, Wilts, a son.

DEATHS

Duncan.—On March 25, 1954, at the Chelsea Nursing Home, Gisborne, New Zealand, Robert Reid Duncan, M.B., Ch.B., D.P.H., formerly of Altrincham, Cheshire, aged 71.

Ham.—On March 28, 1954, Bertie Burnett Ham, M.D., D.P.H., formerly of Australia, aged 86.

Jameson.—On March 31, 1954, at his home, Romeland Cottage, St. Albans, Herts, Harold Parnell Jameson, M.D., M.R.C.P.

Levy.—On March 31, 1954, at his home, The Heights, Marlow, Bucks, Alfred Goodman Levy, M.D., M.R.C.P., aged 87.

McMinn.—On March 31, 1954, at 47, Eaton Place, Brighton, Sussex, Robert Martin McMinn, M.B., Ch.B.

Mitchell.—On March 27, 1954, at Stowmarket, James Robertson Mitchell, M.C., M.B., Ch.B., D.P.H., of Dunallan, Combs Lane, Stowmarket, Suffolk.

Moreton.—On March 31, 1954, at 24, Edensor Road, Eastbourne, Sussex, Reginald Moreton, M.R.C.S., L.R.C.P., aged 81.

Morrin.—On March 22, 1954, at 14, Fitzwilliam Place, Dublin, Eileen Morrin (formerly Dowling), M.B., Ch.B., wife of Francis J. Morrin, M.Ch.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Encephalitis after Immunization

Q.—*How great is the risk of encephalitis following immunization procedures against whooping-cough and diphtheria? Does the risk increase with age, and is it increased if a combined vaccine is given?*

A.—There is no evidence of the occurrence of encephalitis following immunization with diphtheria prophylactic. American workers have reported cases of encephalopathy following injections of pertussis vaccine, but it is very difficult from a collection of case records to estimate what are the chances of developing such a syndrome after pertussis vaccination. It is noteworthy that in Byers and Moll's series[1] twice as many of the cases followed attacks of whooping-cough as followed the prophylactic vaccination. The risk in this country must be extremely small, as, despite the many thousands of young children who have received inoculations of pertussis vaccine in the past few years, recorded cases of post-inoculation encephalopathy have been very rare.[2]

Since most inoculations against pertussis are given in the early years of life it is impossible to say if the risk is greater with older children, although it may be that injections of vaccine in older children will activate a latent infection with a virus that has an affinity for the central nervous system—for example, mumps or herpes virus. There is no evidence that the risk would be greater with a combined prophylactic like pertussis vaccine and diphtheria toxoid, although the apparently greater risk of post-inoculation poliomyelitis following alum-containing combined prophylactics should be kept in mind. It is inadvisable to give pertussis vaccine alone or combined to a child with a history of recent convulsions or within three weeks of vaccination against smallpox.

REFERENCES

[1] Byers, R. K., and Moll, F. C. (1948). *Pediatrics*, 1, 437.
[2] Anderson, I. M., and Morris, D. (1950). *Lancet*, 1, 537.

Spots Before the Eyes

Q.—*What are the causes of "spots before the eyes"? What are their significance and treatment?*

A.—"Spots before the eyes" without any detectable particles moving about inside the eye can occasionally occur in patients suffering from derangement of the vessels which supply the occipital cortex. Such derangement is usually associated with cardiovascular disease elsewhere in the body, and it is unlikely that spasm can account for it in the absence of obliterative changes. A disordered liver, which is commonly blamed by the lay public, may also account for a few cases; but these "spots" are nearly always due to the presence of mobile opacities in the vitreous, and are essentially harmless. Indeed, many patients learn to ignore them when once they are assured that the spots are not of sinister import. Sometimes they are particularly obtrusive when a patient gets up after a long rest, as we can readily appreciate by a simple analogy. If a tumbler of lemon squash stands for a few hours, most of the flakes will settle to the bottom, but rotation or agitation of the vessel will spread these opaque particles, making the contents turbid.

Vitreous opacities are particularly common in myopes, and in all old people, but they are often found on routine examination of patients who had not noticed them. One important cause is choroido-retinitis, in which a shower of inflammatory particles will be launched into the vitreous.

Retinal detachment is another possibility to be borne in mind, but in this condition the patient will probably also complain of a shimmering film seen by the affected eye. Vitreous particles may also be derived from large retinal haemorrhages and intraocular foreign bodies.

There is no ocular treatment for "spots before the eyes" as such. When they are due to constitutional disturbance, treatment on general lines must be given. When the "spots" are due to intraocular disease—for example, retinal detachment—the causative lesion should be attacked. When they are harmless no treatment can disperse them, and the custom of piously prescribing potassium iodide as a remedy is quite useless. "Spots before the eyes," in the absence of general illness, demand a careful eye examination. If no abnormal signs are present, other than mobile vitreous opacities, the patient should be reassured.

Diseases Spread by Breast Milk

Q.—*What diseases of the mother are likely to be communicated to the infant via her milk?*

A.—The answer to this question is quite simple: no diseases are known to be transmitted to the infant via breast milk.

Certain possibilities may be considered, but these are more academic than practical. Staphylococci from a breast abscess might enter the milk, and could infect the child, and for this reason it is wiser to discard or boil milk expressed from an inflamed breast. It is not thought possible for bacteria in the systemic circulation to pass the cell barriers and enter the milk, but it is possible that viruses of small molecular size could do so. There is no evidence that this happens in man. It has been shown that, in specially bred strains of mice, cancer of the breast is transmitted in the breast milk, but nothing of this sort is known in man or other animals. Syphilis might be acquired from the nipple by an infant not infected before birth.

Thrush is frequently acquired from the mother's nipple, not from the milk.

Circumcision in Infancy

Q.—*What are the indications for and against circumcision in the normal healthy baby?*

A.—There are no contraindications to circumcision in earliest infancy. Later, haemophilia is an obvious contraindication.

The indications may be considered under three headings: religious, parental insistence, and paediatric. The first two do not call for any discussion. The third is rare. A preputial orifice so small that micturition is difficult, a long redundant prepuce with repeated ulceration at the tip, or one which is associated with recurring balanitis, and paraphimosis may be regarded as the chief indications. The subject has been well discussed by Gairdner.[1]

REFERENCE

1 *British Medical Journal*, 1949, 2, 1433.

Repeated X-ray Treatment for Cheiropompholyx

Q.—*Is there any danger in repeating x-ray treatment of cheiropompholyx in a case which has already relapsed twice?*

A.—Superficial *x*-ray therapy should be prescribed only by a dermatologist who knows what treatment the patient has previously received. Using unfiltered, fractional dosage—as should be employed—safety depends upon the actual dosage and the spacing of treatments. There is strong evidence to support the view that a total dosage exceeding 1,500 to 2,000 r units should not be given to any one area of skin. In some sites—for example, vulva and perineum—a total dosage of 1,000 to 1,500 r units should probably not be exceeded and such dosage is usually spaced over many years.

Arachnodactyly and Wedge-shaped Vertebrae

Q.—*Is anything known of the inheritance of congenital wedge-shaped vertebrae? I know a father and daughter who both suffer from this condition, associated with mild arachnodactyly. It would be helpful to me to know whether the daughter's children are likely to develop the same condition.*

A.—Arachnodactyly is due to a dominant gene, though there may sometimes be skipping of generations. Sporadic cases also occur; they may be due to dominant mutations. In about half the cases abnormalities of the vertebral column are also present. Very little is known about the genetics of wedge-shaped vertebrae, except that several instances in a family have been reported. As both the father and daughter are affected it is likely that a dominant gene is involved; if so, there is one chance in two that any child will receive it. It may be, however, that owing to possible skipping of generations the chance that any child will actually be affected is somewhat less.

NOTES AND COMMENTS

Male and Female Symbols.—Dr. E. J. THOMSON (Grimsby) writes: Your paragraph on the origin of ♂ and ♀ ("Any Questions?" March 6, p. 596) is obviously no more than a précis of your meditations on the matter, but it does include statements that read like facts, and some of them are fallacious. A less educated—and I refrain from "sophisticated"—eye would see at once that the symbols are simply primitive drawings of male and female genital parts. They were probably stereotyped, and their significance established, long before they were applied to Mars and Venus, and, on this basis, their use in alchemy becomes logical: the hard metal—the spear—is male, and the soft one—the pot—female.

The use of a distinctive part to represent the whole is common in all early art forms, and the gross exaggeration of sexual parts in Palaeolithic statues suggests that inscriptions of that period might yet be found to show just such hieroglyphs as these. This would put the date of origin nearer 10,000 than 2,000 B.C.

OUR EXPERT writes: I do not quite understand Dr. Thomson's difficulties. I am ready to take his word that the symbols ♂ and ♀ were used to indicate the genitals before they were used to designate the planets Mars and Venus, though I know of no evidence for this. As regards his second paragraph there must be a misunderstanding. An *inscription* must be "something written." Not only is there no evidence of writing among men of Palaeolithic culture, but the evidence that we have of their achievements suggests that the conception of writing had not dawned upon them. The earliest efforts that can be reasonably regarded as approaching writing are of the second half of the fourth millennium B.C. and are the work of men of Neolithic culture. This is long after 10,000 B.C. But, leaving the meaning of "inscription" aside, I know of no Palaeolithic painting or carvings of these signs, nor do I see any clear resemblance to ♀ in the exaggeration of the female genitalia in certain Palaeolithic figures. On the other hand, a resemblance of ♂ to the male genitalia may well satisfy those with the eye of faith so inclined, but I should like to have evidence from Palaeolithic paintings that it does so represent them.

Correction.—The leading article on remuneration of consultants (*Journal*, April 10, p. 860) should have read that the weighting allowed to part-time consultants and S.H.M.O.s is to be reduced from one and a quarter sessions to three-quarter sessions, not from one and three-quarter sessions to three-quarter sessions, as stated.

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